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CLOSURE OF THE BRONCHUS FOLLOWING TOTAL PNEUMONECTOMY*

EXPERIMENTAL AND CLINICAL OBSERVATIONS

WILLIAM F. RIENHOFF, JR., M.D.,

JAMES GANNON, JR., M.D.,

AND

IRWIN SHERMAN, M.D.

BALTIMORE, MD.

FROM THE DEPARTMENT OF SURGERY, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

THE EVER INCREASING APPLICATION of total pneumonectomy to the treatment of malignant and inflammatory diseases of the lung, places on those particularly interested in this procedure the grave responsibility of increasing the margin of safety. The problem considered in our discussion is that of closure of the primary bronchus.

A review of the literature on experimental pneumonectomy impresses one with the fact that, to a great extent, the majority of the authors have had little knowledge of the possible clinical application of the various experimental procedures described. Due appreciation, however, must be accorded those earlier workers whose stimulating reports have given so much impetus to the advances that have been made, not only in experimental but in clinical pneumonectomy, since Glück's work in 1881. It is, of course, well known that anatomic differences exist between the laboratory animal and the human being which, in large measure, vitiate many of the suggestions that have been made in regard to bronchial suture. On the other hand, the available clinical data on closure of the primary bronchus following total pneumonectomy are very meager, and it is for this reason that we are presenting our observations. We hope that suggestions will be made to aid us in the solution of the problem, and that those whose results have been more successful along these lines will report them. We realize that all too frequently our efforts have been unsatisfactory.

In order to contrast previous experimental observations with our own, we shall present our laboratory data before reviewing the literature. In this

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way the difference in the technic employed in our series of experimental pneumonectomies, and that of others, will be available for a comparative analysis. It is for this reason that we have chosen to reverse the usual order of such a report.

EXPERIMENTAL PNEUMONECTOMY

The various operations were performed under as nearly identical circumstances as possible. Therefore, the same anesthetist (T. S.), operator (W. F. R.), and assistants (J. G., Jr., and I. S.) carried through all the details of each experiment from the beginning to its final conclusion, thus making for consistency in technic. The dogs were selected to correspond as closely as possible in age and weight; generally speaking, they were young adult animals of medium height, weighing on an average about eight kilograms. A relative uniformity in size and age assures one of a considerable degree of similarity not only in the diameter of the bronchus, but in the flexibility of its walls and the malleability of the cartilaginous rings.

Our experimental observations extend over a period of more than three years, during which time over 200 dogs have been subjected to total pneumonectomy. In addition to the technic which had been employed in the past by various observers, in several of our earlier series recourse was had to methods for the closure of the primary bronchus that had, heretofore, not been used by other investigators. The work of previous authors on experimental pneumonectomy was repeated with, generally speaking, comparable results. It was soon realized that the methods used in the past, in a high percentage of instances, were imperfect, not only in experimental pneumonectomy, but also from the standpoint of clinical application.

After a careful and critical analysis of our operative results and those of previous observers in experimental pneumonectomy, the problem which we faced seemed to be divided into two main parts: First, to develop a method of closure of the primary bronchus of the dog that could be used successfully in a high percentage of experimental pneumonectomies, either for the right or the left side; and, second, that this method should be one that could also be applied to the closure of the primary bronchus in the human being. A review of the literature on experimental peumonectomy reveals the fact that the great majority of observations made on the closure of the primary bronchus have dealt with the left side. In the dog, as in the human being, the left bronchus, because of its greater length, lends itself more readily to the various methods of closure which have been advocated in the past. On the right side, however, the primary bronchus is very short, consisting, indeed, of only one cartilaginous ring. Because of this shortness a simple circumferential ligature or inversion of the bronchus, after the manner of Willy Meyer, was found not to be a feasible procedure. This anatomic difference has made it impossible to use other proposed methods which could be applied to the left bronchus. In our final series of experimental pneumonectomies the two dif-

ferent methods of closure adopted were workable in the dog, not only for the left bronchus but also for the right.

Preliminary Experiments.—In successive series of animals, previously reported methods employed in the closure of the primary bronchus were repeated and also certain means of occlusion were tried that had not been utilized by others. Constricting and transfixing ligatures of silk, different sized steel and silver wires, all forms of catgut, silver bands, fascial ribbon alone and in combination with braided silk, were made use of, only to find that in many animals the ligature would cut through the bronchus between the fifth and the tenth day. Particularly was this true on the right side, but regardless of the side the bronchus always opened proximal to the ligature. In a small series of animals the left bronchus was filled with litharge, lead oxide, and glycerine, between two temporary ligatures before the lung was amputated. This substance was injected in a semifluid state by means of the old-fashioned paraffin syringes, and, after setting for a few moments, became rock-like in hardness. After amputation, the bronchus was closed with interrupted sutures distal to the injected mass. A high percentage of the bronchi, occluded in this manner, leaked about the site of injection as the walls dilated about the foreign body. After many other trials the use of interrupted mattress sutures was found to be the most satisfactory method of closure.

Final Experiments.—Experimental Operations in the First Series of 36 Dogs: Total pneumonectomy was performed in 18 animals on the right side and in 18 on the left side. All animals recovered from the operation, living for a period of over four weeks, and some as long as six months. The series was begun early in the fall. We were fortunate in losing only two animals from distemper but, in all, including the two in which the autopsy findings were typical of distemper with bronchopneumonia, the primary bronchus of the operated side was perfectly healed. The two animals which died of distemper had been operated upon more than two months before death.

A description of a typical experiment is as follows:

The animal was given a preoperative injection of 16 mg. of morphine hypodermically about one hour before operation. It was anesthetized by drip-ether through an ether cone, until it had reached a sufficient depth of anesthesia to enable an intratracheal tube to be inserted without difficulty. This tube was sterile, and care was taken to avoid, as nearly as possible, all contamination during insertion, and to introduce the tube only part way down the trachea so as to prevent contamination of the primary bronchi. The tube was firmly fixed to the lower jaw by means of a mouth gag and then connected with a continuous flow of air, which by proper adjustment could be completely or partially bubbled through ether. The intratracheal tube being smaller than the trachea, positive intratracheal pressure could be obtained only by the anesthetist compressing the trachea about the tube. A mercury manometer, which constantly registered the intratracheal pressure, was connected with this intratracheal catheter. The side, either right or left, to be operated upon was shaved and thoroughly cleansed with soap and water, then washed with ether, followed by half-strength iodine and alcohol. Great care, from the technical standpoint, was observed in all steps because of the well known fact that the pleural cavity in dogs is easily infected.

An incision was made (Fig. 1) over the fourth interspace which, in our experience,

FIG. 1.—Demonstrating location of skin and muscle-splitting type of incision for experimental pneumonectomy.

usually corresponded to the point of maximum impulse of the heart and could easily be determined either on the right or left side. The incision usually extended for a distance of about four centimeters on the dome, so to speak, of the chest, about midway between the dorsal and ventral lines. The platysma muscle was cut through along the line of incision. The latissimus dorsi, as noted, was cut along the course of its fibers, which is perpendicular to the incision. The serratus muscle was separated as the incision was carried through the intercostal muscles parallel to the ribs. In this manner, a gridiron

incision of minimal length was made which caused little damage to the subcutaneous structures when the thorax was entered. After the lung was delivered (Fig. 2) the sequence of ligation of the various vessels was slightly different, depending upon whether the right or the left side was operated upon. On the left side (Fig. 4), as the pulmonary artery passes over the posterosuperior surface of the left primary bronchus, this vessel was ligated (Figs. 2 and 3) and divided. The superior, middle, and inferior pulmonary

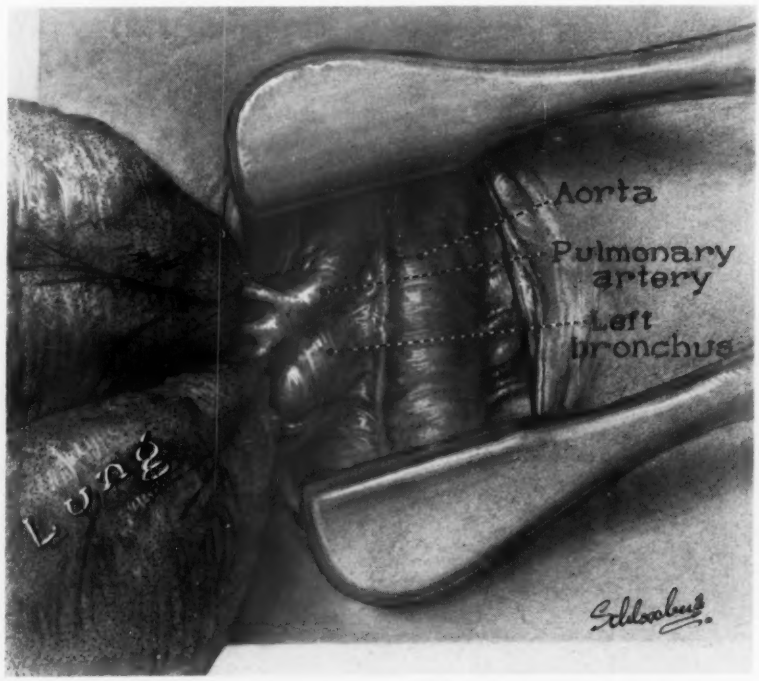

FIG. 2.—Left lung delivered from thoracic cavity. Note length of left bronchus and position of left pulmonary artery, also type of self-retaining retractor.

veins were then secured with fine silk ligatures, as were the small arteries on the dorsal surface of the bronchus. The peribronchial areolar tissue on the superior, dorsal, and inferior surfaces was cut across but not dissected back from the proposed line of incision across the bronchus. In nine of the 18 instances, in which the lung was removed on the left side, the bronchus was amputated proximal to the first departing branch, and in the other half at the point of departure from the trachea. Before amputation a row of four to six interrupted mattress sutures was placed postero-anteriorly, each loop of the mattress suture, encircling one cartilaginous ring. Thus the posterior membranous portion was made to approximate the anterior cartilaginous rings and the amputated end of the primary bronchus was flattened (Fig. 4).

It is to be recalled that in the dog the bronchial rings form more of a complete circle than in the human being, and in order to fit the posterior membranous portion into the arch of the anterior cartilaginous ring in the dog the most ventral ends of these rings must be angulated upon themselves and approximated to the anterior portion (Figs. 4 and 5). This is not true of the human being, where the ring forms more of a semicircle. However, one row of interrupted mattress sutures was so placed and then the bronchus amputated beyond this suture line. It is to be noted that there was no crushing of the bronchus with clamps nor was any chemical or thermal cautery used,

nor any attempt made to destroy the mucosa either under the suture line or distal to it. The intratracheal pressure at this point was always increased to at least 80 Mm. of pressure, which caused a hyperexpansion of the lung on the unoperated side. This hyperexpansion would invariably demonstrate the fact that the amputated bronchial stump was sealed airtight by the sutures. If by any chance there was some hissing or other evidence of leaking air, another interrupted mattress suture was inserted. The mediastinal pleura was then sutured over the amputated end of the bronchus with a few interrupted silk sutures covering the raw surface of the operative field in order to render the operation a more finished procedure. The routine closure of the chest was accomplished by the use of two pericostal sutures of No. 10 braided silk (Fig. 6) which were drawn home and tied as the anesthetist expanded the contralateral lung, expelling as much air from the thorax as possible. Two, or at the most three, interrupted silk sutures were employed to close the opening in the latissmus dorsi and a continuous subcuticular and cuticular silk suture was used in the skin. No dressing was applied to the wound (Fig. 7). Silk sutures were used throughout.

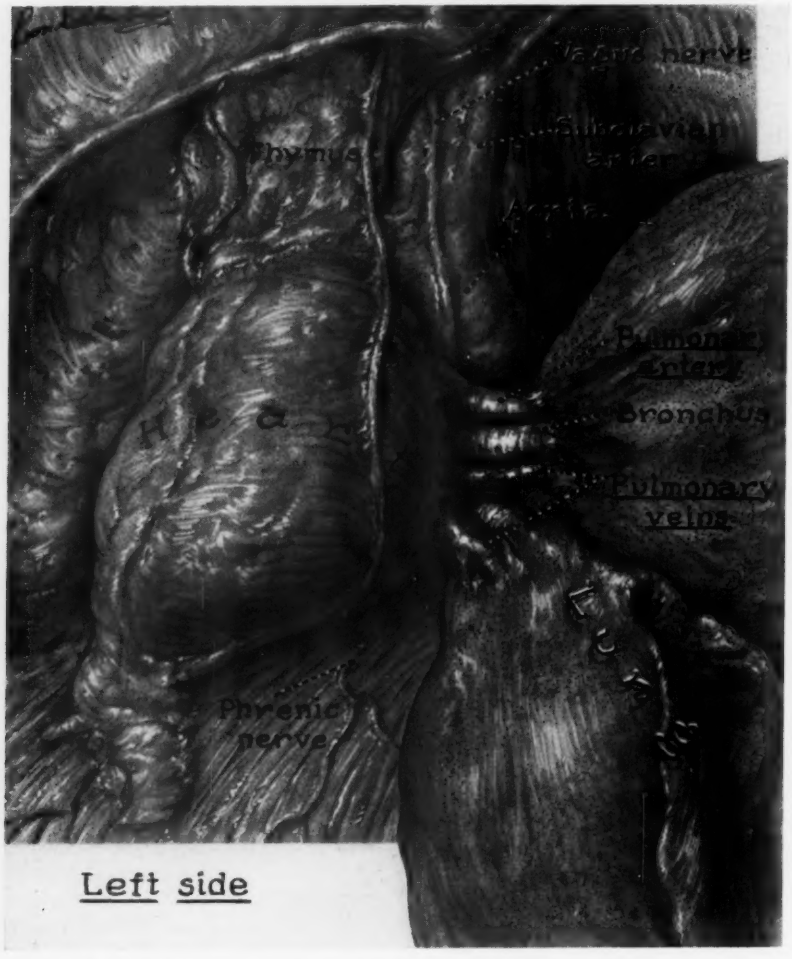

FIG. 3.—Anatomic demonstration of ventral surface of left lung, showing the hilar structures.

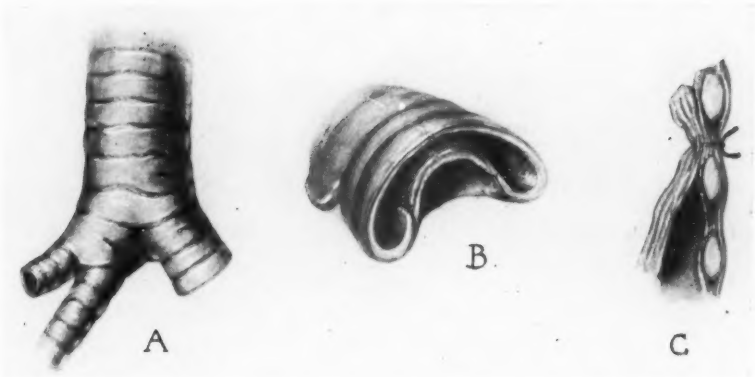

FIG. 4.—A. Representing lower end of trachea and bifurcation into right and left bronchus. A single cartilaginous ring composes the right main bronchus which bifurcates into the ascending and descending branches. The left bronchus has not been drawn to its full extent, but, as indicated, is longer and smaller in diameter than the right bronchus.

B. Representing cut end of bronchus, demonstrating the extent to which the cartilaginous rings almost completely surround the bronchial tube, forming more than a semicircle with a small posterior membranous portion, less than in the human being.

C. Method of closure of dog's bronchus with interrupted mattress sutures, opposing posterior membranous to anterior cartilaginous portion.

The operation on the right side differed from that on the left only insofar as the sequence of ligation of the pulmonary vessels was concerned (Fig. 8). It is somewhat easier on the right side to ligate first the upper and middle pulmonary veins before attempting to tie the pulmonary artery. The latter lies deeper on the ventral surface and can be readily secured after the veins are ligated. The treatment of the bronchial stump was the same as on the left side.

Due to the fact that the right primary brochus consists of only one tracheal ring, the use of interrupted mattress sutures for experimental, total right pneumonectomy proved to be a most satisfactory method. It is impossible, even in the dog, to invert this stump or to use a circumferential ligature on it, as the latter will invariably cut through because of tension.

The dogs were returned to the cages always in excellent condition. There was occasionally some hyperpnea following operation, but very little. The animals were placed on a regular diet the following day. Except for the two that died of distemper, there were no fatalities.

The length of time consumed in these experimental pneumonectomies was never over 20 minutes. The same instrument table was used at each operative session, at which time a minimum of two dogs were always operated upon, one on the right side and one on the left side.

Roentgenograms of the chest were taken 24, 48, 72, 96, and 120 hours following operation to determine the rapidity of the compensatory dilatation of the remaining lung, manifested by pushing of the heart and the mediastinal structures to the operated side, with subsequent obliteration of the dead space resulting from the removal of one lung. In all instances, after 48 hours, the heart was completely displaced to the chest wall of the operated side. In some animals this occurred in 24 hours. There was never an accumulation of fluid in the chest of the operated side, and no instances of infection of either

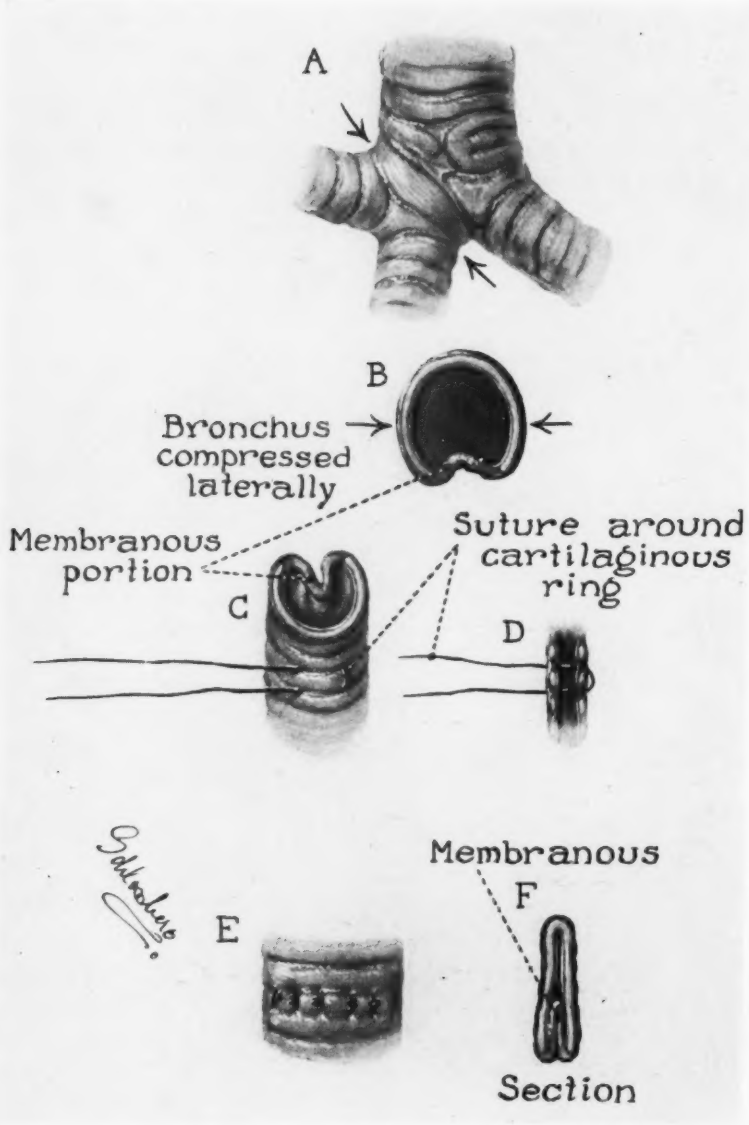

FIG. 5.—A. Demonstrating the relative length of the right and left bronchus. The right is seen to be composed of a single cartilaginous ring.

B. Cross-section of bronchus, again showing the proportion of the membranous to the cartilaginous portion.

C. Insertion of mattress sutures laterally so as to compress the walls of the bronchus laterally instead of anteroposteriorly.

D, E, and F. The completion of this approximation.

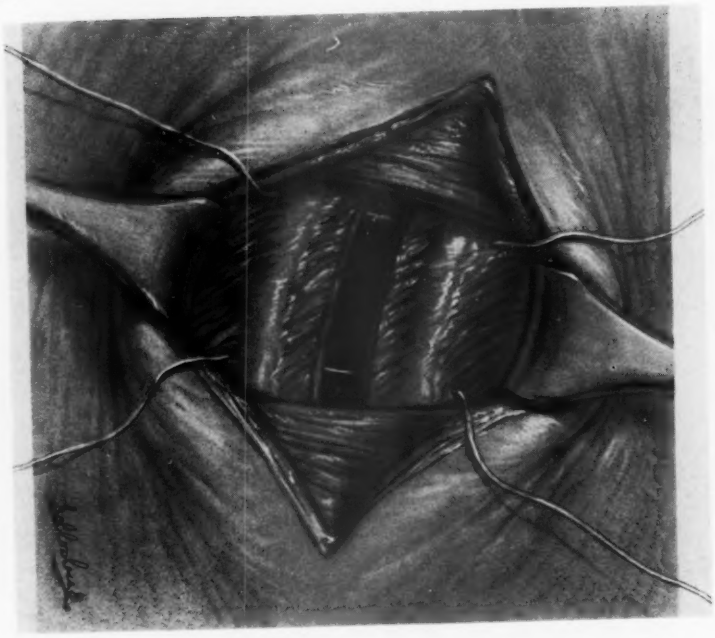

FIG. 6.—Closure of the thoracic cavity with pericostal sutures.

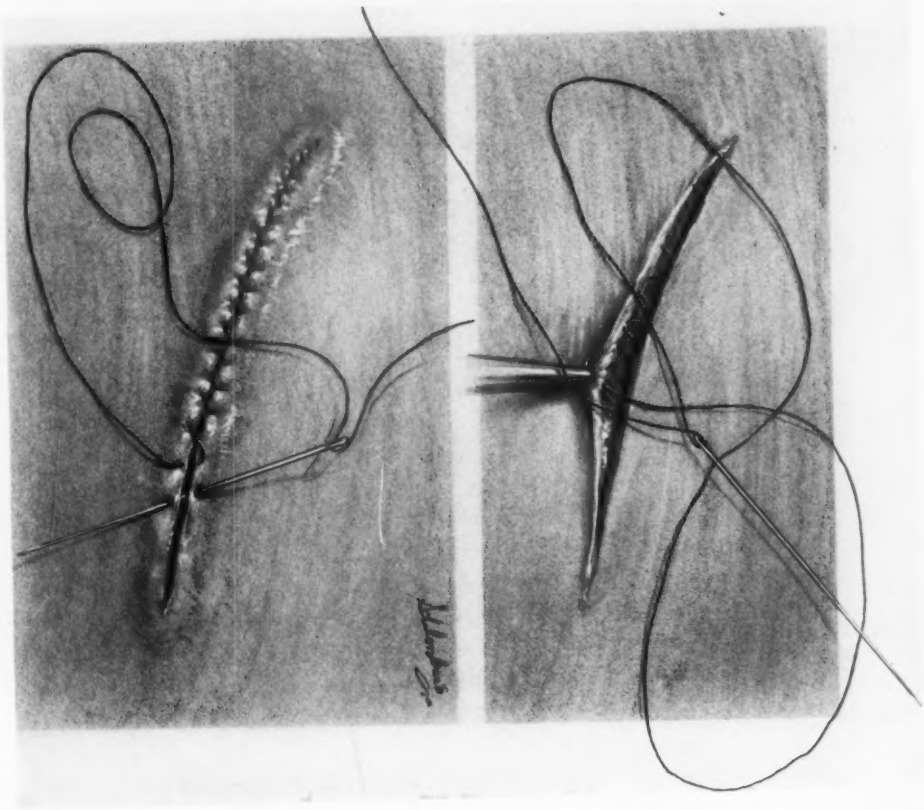

FIG. 7.—Subcuticular and cuticular sutures in the skin. Actual length of incision employed is of the same length as illustrated.

the wound or the pleural cavity occurred in the entire series. From time-to-time Dr. E. N. Broyles performed bronchoscopic examinations on various animals and made lipiodol bronchograms, which showed complete healing of the bronchial stump.

In this series, no animals were sacrificed in less time than four weeks, and some were allowed to live as long as six months. On account of the shortage of cage space and the expense of keeping the animals, there was a necessity for sacrificing them within a reasonable time after operation when the bronchus was unquestionably healed solidly. After lipiodol bronchograms had

FIG. 8.—Anatomic demonstration of the right thorax, mediastinum and hilus of right lung in the dog.

been made of each animal they were sacrificed in a routine manner. The chest was opened on the operated side and filled with water. With the tracheal tube in place and connected with a mercury manometer the intratracheal and bronchial pressure was raised to 200 Mm. of mercury and in some instances to 300 Mm. There was, of course, a hyperdistension of the remaining lung. Due to the fact that the healed bronchial stumps were under water, any bubbling of air could be readily detected. There was no instance in this series in which the bronchial stump leaked.

It is to be noted, here, that a pressure of from 8 to 10 Mm. of mercury

would distend the unoperated lung to its maximum capacity at the completion of the operation. This fact was determined by inflating the lungs of animals in earlier preliminary experiments. The amount of pressure necessary to fill the chest depends, of course, on the size of the dog; but as stated in the beginning, our dogs were more or less of uniform size and weight so that an average pressure required for such distention could be determined within

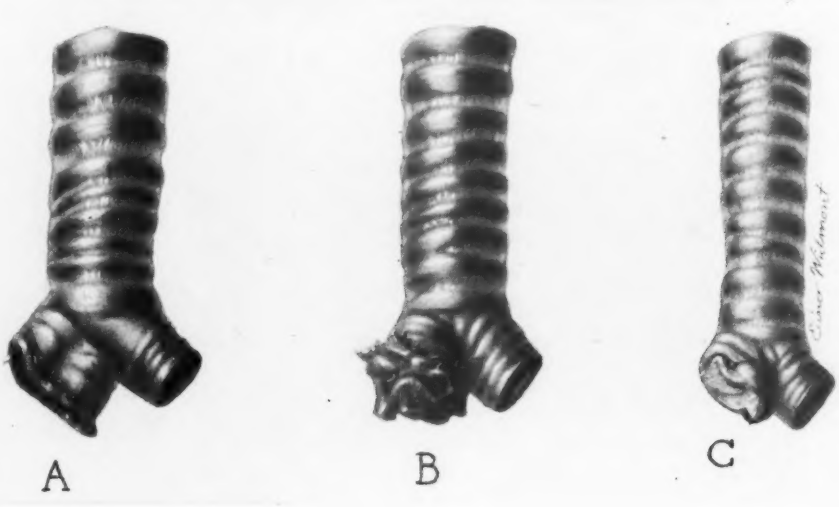

FIG. 9.—Illustration of gross specimens dissected at autopsy, showing three distinct types of healing encountered after suture of the bronchus, as described in the first series of 36 dogs.
A. The conical-shaped bronchus that has healed as it was sutured at operation.
B. The sutures have cut through the wall and the open end is healed with a fibrous tissue mass. Sutures may be seen to lie in the peribronchial tissue.
C. Sutures have cut through, evidently discharged into the lumen of the bronchus. No evidence of them in the peribronchial tissue. Walls of bronchus completely separated and cut end of stump healed over by membranous sheet of tissue.

reasonable limits. The healed bronchial stumps were carefully dissected and preserved in either formalin or van de Grift's solution. Serial sections were cut and stained with hematoxylin and eosin.

Experimental Results in the First Series of 36 Dogs.—These showed plainly, in the gross, that on the operated side the mediastinal pleura was everywhere smooth and glistening and that only a slight dimpling, when a pull was made on the trachea, revealed the buried healed stump of the bronchus. In every instance the mediastinal pleura had healed completely with an almost invisible scar. In all specimens the bronchus formed a rounded stump covered externally with fibrous tissue. When the internal surface of the healed bronchial stump was examined it was at once noted, from the gross appearance, that the healing differed. In only 18 per cent (Figs. 9 and 10) was the bronchial stump conical in shape, with the appearance of being healed as it had been sutured at the time of operation, the tip of the cone being at the point of approximation of the anterior and posterior surfaces. This was considered the ideal type of healing. In another small group, 16 per cent, the

lumen of the bronchus appeared undiminished to the end, across which there was a flat membrane that completely closed the cut end of the bronchus, very much as the skin covers a drum. It was noted, also, that in these instances there seemed to be a central elevation with two lateral depressions at the healed end as one viewed the bronchus from the inside, as shown in Fig. 10. This elevation appeared to bisect the membrane extending across the circumference of the bronchial lumen, with two pits on either side. In nine per cent, the end of the bronchus seemed to be filled with a mass of fibrous tissue, the inside surface of which was very irregular and resembled, at times, papilloma-like formations (Fig. 10).

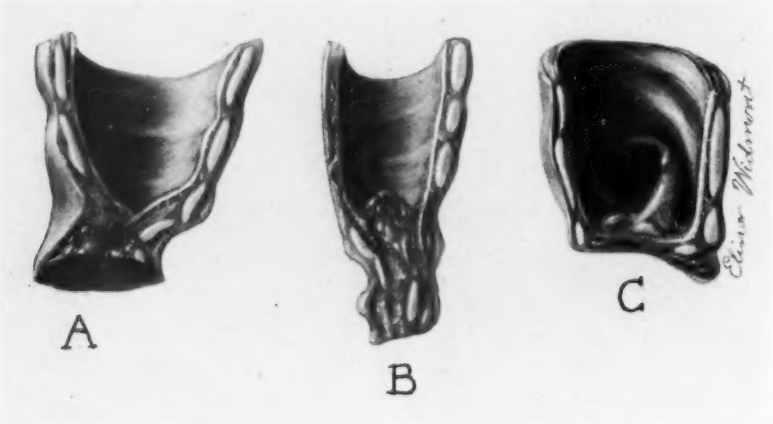

FIG. 10.—Cross-section of gross specimens, shown in Fig. 9, A, B and C.
A. Bronchus healed as sewn at operation.
B. Walls of bronchus, separated as a result of cutting of silk sutures and open end healed by the formation of a fibrous tissue plug or mass occluding the lumen. The internal portion of the mass is covered with bronchial epithelium.
C. Sutures have cut through in the lumen, two may be seen. Bronchial walls have separated and the open end has been occluded by a thin membrane stretching between the cut cartilaginous rings. Internal surface of cylindrical end irregular with elevated ridges flanked by depressed areas on either side of ridge.

In the majority of animals, 57 per cent, the manner in which the bronchial stump healed proved to be a combination of the three types mentioned above. From the gross appearance the bronchus would be conical in one portion of the healed end while the remaining half appeared to be blunt or rounded and covered over by a thin membrane. In instances in which the bronchus was not entirely conical but had healed partially as sewed, silk sutures were usually visible beneath the lining epithelium of the internal surface of the bronchial stump, and were always proximal to the healed edge of the bronchus. In several instances these sutures had ulcerated part way through the lining epithelium of the bronchial stump, but had not been discharged. Some were nearer the healed end than others, but all were proximal to the ultimate line of healing (Fig. 10). The internal surface of some of the healed stumps, that were not conical but rather cylindrical, was often indented by small tangential bands or ridges (Fig. 11), as though the epithelium had grown over

some protruding mass that had plugged the end of the bronchus. Sections through various diameters of the bronchi were cut *seriatim* so that a microscopic study could be made of the different types of healing. From a study of the microscopic sections it was found that the bronchi had healed, as anticipated from an examination of the gross specimens, in a manner that permitted classifying them into four main groups: First, the ideal or conical type, in

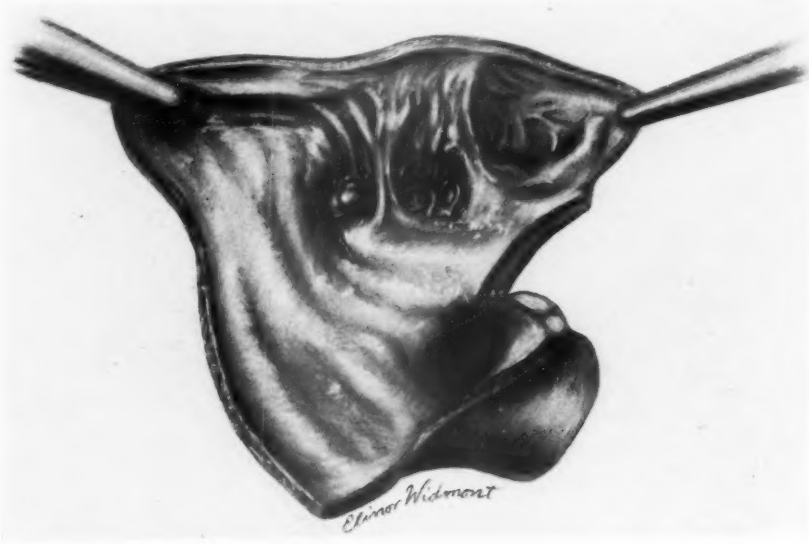

FIG. 11.—Inner surface of amputated stump of right bronchus (dog sacrificed after four weeks) shows epithelization having occurred over irregular internal surface of fibrous tissue mass occluding the end of the bronchus.

which the bronchus had remained closed as sutured at operation and in which all sutures had remained in their original position without cutting through (Fig. 12). This group comprised 18 per cent of the animals. The second division included 16 per cent, in which all the sutures had cut through and the bronchus had opened completely. The cut end had been closed only by a membrane which was composed of bronchial epithelium and subpleural and contiguous areolar fibrous tissue contributed by the bronchial wall itself (Fig. 13). In nine per cent there appeared to be a firm connective tissue plug which filled the end of the bronchus, the sutures as placed at operation had cut through, the bronchial walls had separated, and the portion of the bronchus distal to the suture line was closed by means of this tampon (Fig. 14, a and b). This consisted of white fibrous connective tissue, capillaries, and lymph follicles, as well as apparently atrophic, nonviable portions of cartilage forming part of the bronchial wall distal to the row of mattress sutures. In the peribronchial portion of this mass of fibrous tissue encysted silk sutures were often found. These probably were those mattress sutures which had cut through the walls of the bronchus, but had not ulcerated into the lumen and hence were not coughed up. Such cysts consisted of small abscesses lined

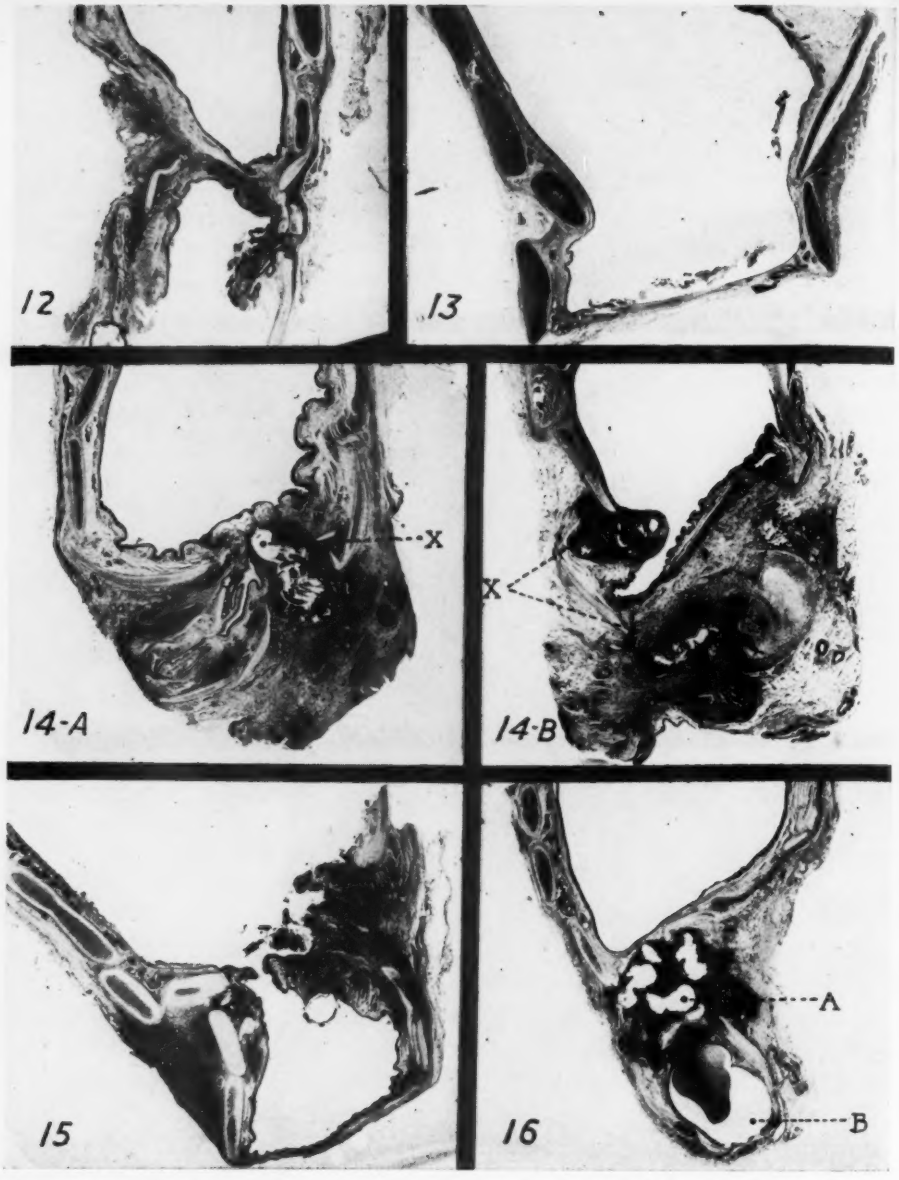

FIG. 12.—Dog A-2 (section 8 micra, x6): Dog sacrificed after four weeks. Conical bronchial stump healed as sutured at operation. Note viable bronchial cuff distal to healed stump. Ideal type of healing such as this occurred in only 18 per cent; shown in gross (Figs. 9 and 10A).

FIG. 13.—Dog A-3 (section 8 micra, x5): Dog sacrificed after four weeks. Type of healing shown in gross specimens (C. of Figs. 9 and 10). Bronchial walls opened, healing occurred at end of amputated stump. Note flattened regenerated epithelium and absence of mucous glands in the portion of the occluding membrane that has been drived from subpleural and bronchial connective tissue.

FIG. 14.—A. Dog A-23 (8 micra, x6): Dog sacrificed after four weeks. Healing of bronchial stump has occurred as in Figs. 9 and 10, Type B. Silk sutures have cut through and shown at X to lie in a cyst-like microscopic abscess. Note the bronchus occluded by fibrous tissue mass.

B. Dog A-27 (8 micra, x5). Dog sacrificed after four weeks. Cutting silk sutures seen at X. Fibrous tissue mass has plugged end of bronchus through which epithelium has grown. Bronchial walls had opened widely as a result of cutting silk, one suture being extruded into lumen.

FIG. 15.—Dog A-9 (8 micra): Dog sacrificed after two months. Shows lumen of bronchus almost completely closed by diaphragm of bronchial wall at the site of the suture line. However, sutures have cut through, one may be seen in the lumen above diaphragm. Bronchus healed at cut end, by membrane derived from bronchial and subpleural connective tissue. Open communication between lumen of main bronchus and cut end.

FIG. 16.—Dog A-2 (8 micra, x6): Dog sacrificed after eight weeks. Shows cylindrical stump of bronchus healed by fibrous tissue plug with two forms of cysts: First, microscopic abscesses containing sutures which have cut through the wall and separated the healed stump of bronchus from the remaining viable cuff which has in itself healed and formed a cyst-like structure lined with bronchial epithelium. The microscopic abscesses are labeled A, and the cyst formed from the cuff of bronchus distal to the suture line is labeled B.

mainly with small and large mononuclears, some giant cells, and polymorphonuclear leukocytes. There were also some cysts which were lined with bronchial epithelium that probably represented the epithelial lined portion of the bronchus which lay distal to the suture line. This epithelium seemed to persist whereas the cartilage appeared to atrophy.

In 57 per cent the healing of the bronchus took place in a manner that might be considered a combination of the above described three main types. Part of the bronchus would be healed as sewed at operation while another part might be filled with a fibrous connective tissue plug over which the epithelium had grown and had occluded the bronchus. Another combination proved to be one in which a portion of the bronchus had opened while a small part that had healed as sutured remained as a persistent shelf. In some sections this shelf would almost but not quite cover over the lumen of the bronchus, leaving a small opening into a cyst-like structure distal to the original suture line. This cyst-like structure had been formed by the apposition of the mediastinal pleura and fibrous tissue across the open end of the distal cuff of the bronchus (Fig. 15.) The various combinations of this type of healing are shown in Figures 14 A and B, 15, and 16.

This series, therefore, demonstrated to us that, regardless of the perfect end-results of the experiments as far as the survival of the animal was concerned, and despite the care in the technic as well as in the method of suture, there will be a high percentage of animals in which the bronchus will open entirely, or in part, because of cutting through of the sutures, and that one could not depend upon either the type of suture or the method of its insertion to close the bronchial stump completely and permanently. In this series of experiments, had it not been for the fact that the mediastinal pleural and also the peribronchial connective tissue had participated in the closure of the bronchus, there would have been many instances in which the bronchus would have leaked and the animal would have succumbed.

It was concluded from this series of experiments that the technic of closure of the bronchus should comprise the general surgical principles of the minimum of trauma and the maximum of preservation of the viability of the tissues. Healing of the bronchus is mainly accomplished by a proliferation of peribronchial and submucosal fibrous tissue together with a growth of granulation tissue derived from the nonserous surface of the mediastinal pleura. An additional contribution made by the bronchus is the layer of epithelium which seems to be very vigorous and needs only a viable base upon which it may grow. This viable base may be supplied by an occluding mass of granulation tissue in the mouth of the bronchus or a delicate layer derived from the nonserous surface of the mediastinal pleura.

Experimental Operations in the Second Series of 48 Dogs.—It occurred to us that it would be interesting to determine whether healing of the amputated bronchial stump would take place if only the mediastinal pleura was sutured across the cut end of the open bronchus, without any attempt to close this open end with either suture or ligature. Accordingly, a series of 48 dogs

were operated upon, the right and left side alternately, thus affording 24 instances of right total pneumonectomy as well as left. In this series there were two deaths from distemper at the end of two and one-half weeks; in both instances the bronchus was completely healed and the lesions of distemper were present and typical.

In this series of 48 animals, 36 were allowed to live more than four weeks, excepting the two that have been mentioned as having died of distemper, while ten were sacrificed after 24, 48, 72, 96, and 120 hours in order to determine the amount of increase in intratracheal pressure that the recently closed bronchus would withstand.

In previous experiments in which the lungs were distended with air in both living and dead animals it was found that an increase in intratracheal pressure up to 10 mg. of mercury could cause an expansion of the lungs sufficient to fill the thoracic cavity completely.

In 26 animals of our second series following total pneumonectomy, intratracheal pressure readings were recorded at the time of the completion of the operation and when the animals were sacrificed. Immediately following total pneumonectomy, the contralateral lung was routinely overdistended, in order to ensure proper oxygenation as well as to secure apposition of the cut end of the bronchus to the mediastinal pleura covering this end. It is to be recalled that the dogs used were of as nearly uniform weight as possible, averaging about eight kilograms. To our surprise, the mediastinal pleura would not allow the escape of air from the open end of the bronchus until the intratracheal pressure was above that required to hyperdistend the unoperated lung. The escape of air was recognized by a faint hissing sound audible at the time of operation. The lowest pressure withstood at the completion of the operation was 12 Mm., the highest 50 Mm., and the average 24 Mm. In this second series of 26 animals sacrificed after four weeks the bronchi withstood intratracheal pressure up to 300 Mm. without leaking. The readings were made with the healed end of the bronchus under water. Since above 300 Mm. of mercury pressure the unoperated lung will rupture in some areas, this figure was considered evidence of complete healing. In ten instances the animals were sacrificed after 24, 48, 72, 96, and 120 hours following operation. In two in which the postoperative duration of life was 24 hours, the pressure endured at time of operation was 12 Mm. whereas the postmortem pressure was 300 Mm.! Three animals sacrificed after 48 hours advanced from operative readings of 12, 10, and 20 Mm. to 300, 200, and 80 Mm. The remaining five dogs revealed almost identical readings. Two of them were killed after 72 hours and the remaining three at the end of 120 hours. The operative pressure sustained was between 30 and 40 Mm., whereas the bronchi did not leak when the intratracheal pressure was run up to 300 Mm. at the time the animals were sacrificed. This unexpected tenacity of the open cut end of the bronchus to the overlying mediastinal pleura and areolar tissue depends primarily, as will be demonstrated, upon the presence in the end of the bronchus of a fibrinous and later a fibrous plug, and, secondarily,

upon the apposition of the end of the amputated bronchus to the nonserous surface of the mediastinal pleura. The constant hyperdistention of the remaining lung maintains the open bronchial tube in constant contact with the covering areolar tissue.

In 30 animals in which cultures were made from the primary bronchus at the time of operation, 18 were infected; *B. bronchisepticus* was present in

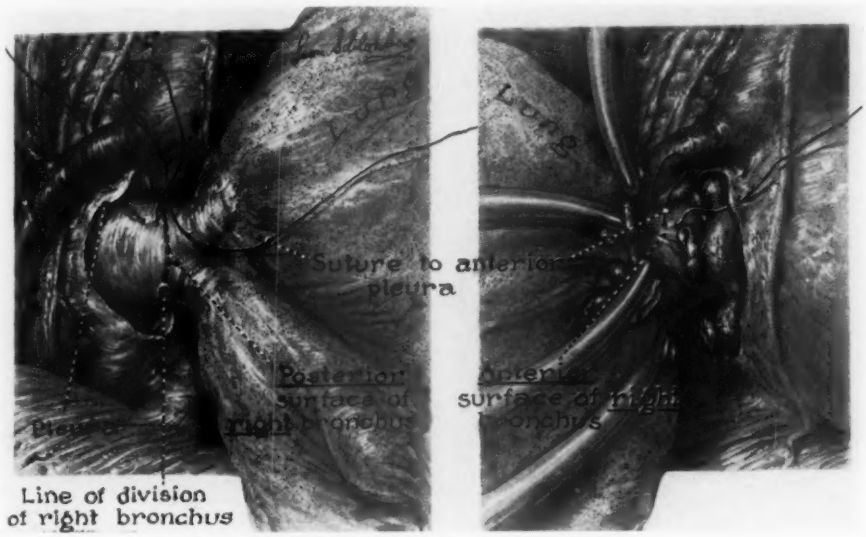

FIG. 17.—Illustrating a method of placing presection sutures before amputation of right primary bronchus in type of closure used in second series of experimental pneumonectomies. Azygos vein may be seen at upper portion of primary bronchus.

11, *B. subtilis* in five, and *Staphylococcus albus* or *citreus* was grown with *B. anthrax* and *B. coli* in one each.

The technic employed in these experiments was as follows:

The total pneumonectomy was performed just as in the first series of experimental pneumonectomies, except that no suture was used to close the end of the bronchus on either the right or the left side. The nonserous surface of the mediastinal pleura was sutured across the opening of the proximal end of the amputated bronchial stump. This was accomplished by means of interrupted presection silk sutures through the lips of the incised mediastinal pleura from the posterior to the anterior aspect of the bronchus; at the same time a very small bite of peribronchial fibrous tissue was taken on the posterior and the anterior surface of the bronchus so that the mediastinal pleura would be held snugly against the cut open end of the bronchial stump (Figs. 17 and 18). Three such sutures were placed and the bronchus was amputated. Since the animals, of course, cannot breathe until the sutures are tied and the edges of the mediastinal pleura approximated over the cut end of the bronchus, as little time as possible must be consumed in performing this type of operation.

On the left side, three pleural sutures usually sufficed; on the right side, sometimes an additional stitch and occasionally two were required. In not one instance was any difficulty encountered in securing close apposition of the mediastinal pleura to the cut end of the bronchus. The anesthetist, by increasing the intratracheal, and thereby the intrapulmonic pressure in the unoperated lung, caused an immediate hyperdistention of

the remaining lung which resulted in displacement of the film-like mediastinal pleura and hilar structure to the operated side. This displacement, by virtue of its force alone, brought the end of the bronchus in close apposition to the mediastinal pleura. However, in order to ensure a snug approximation of this pleural surface to the cut end of the

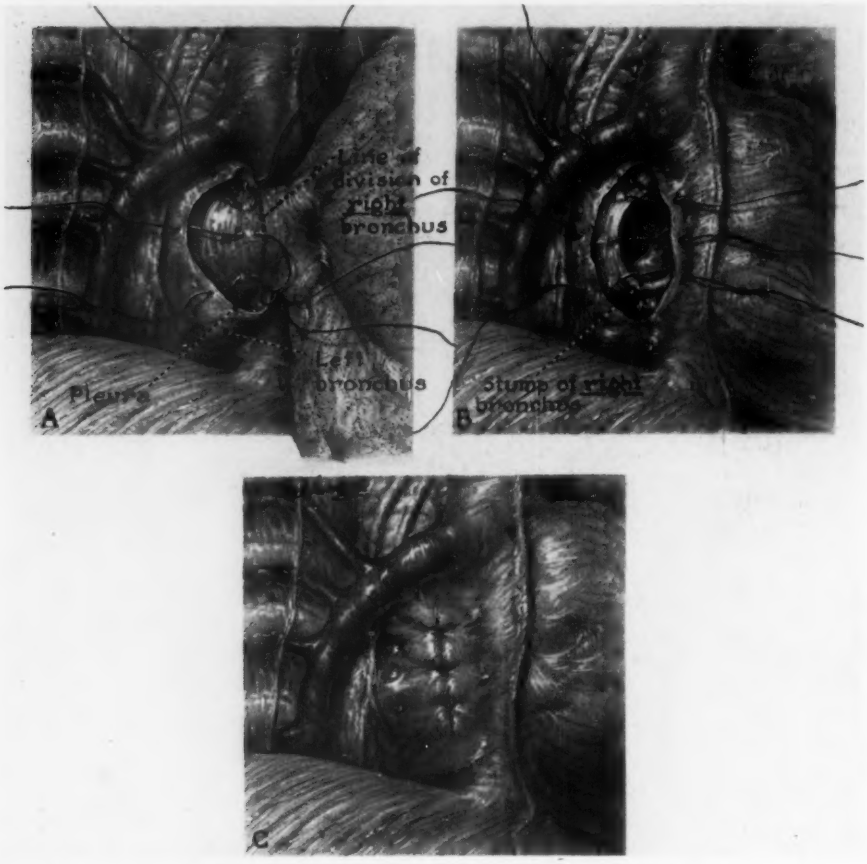

FIG. 18.—Method of closure of mediastinal pleura over open cut end of bronchial stump.

bronchus, the stitches which brought together the incised lips of the mediastinal pleura should at the same time include the slightest bit of the peribronchial connective tissue, situated proximal to the cut end of the bronchus. It is to be noted here that the film-like character of the dog's mediastinum, which is nothing but a simple pleural membrane, allows in proportion a great deal more expansion of the remaining lung, and, therefore, a stronger apposition of its mediastinal pleura to the cut end of the bronchus than would occur in the human being. It would, therefore, seem more important in the human being to secure this approximation of these two structures by sutures.

The manner in which the bronchi healed, as determined by gross inspection, was attended by the formation of less scar tissue, except about the end of the tube, than in the sutured bronchi. The mediastinal pleura as seen from the inside of the thoracic cavity was everywhere smooth and glistening.

Serial sections were made of the amputated bronchial stumps at different

stages in the healing process, and showed that in the first few days the mechanism of healing was very similar, but that the end-results varied somewhat in their gross and microscopic appearance.

The bronchial stump of the animal sacrificed after 24 hours appeared, grossly, to be plugged with an inverted mushroom-shaped clot, resembling in many respects an hematoma (Fig. 19). This coagulated mass of tissue

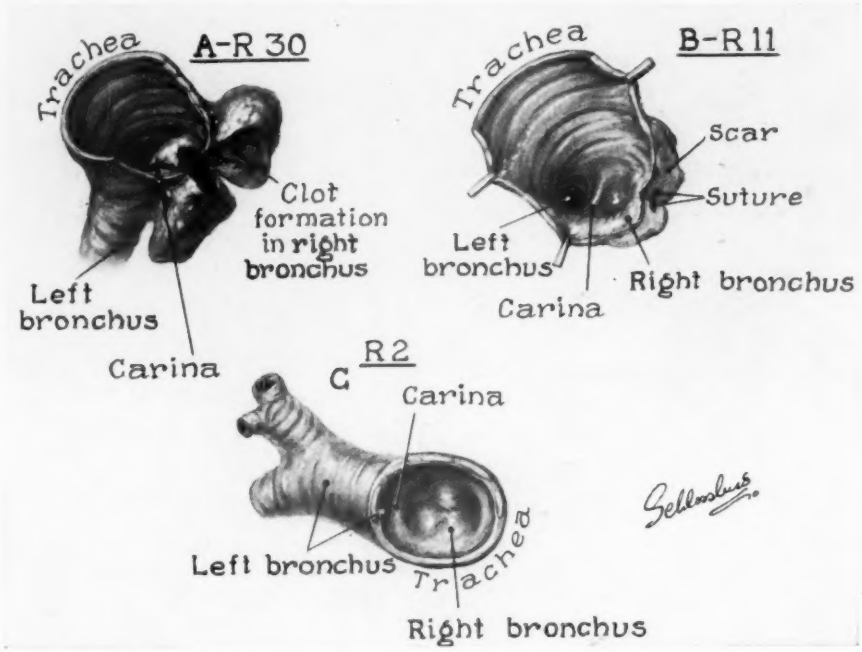

FIG. 19.—Type of healing observed in gross specimens of second series, in which no sutures were used to close the amputated bronchial stump. A, R-30, sacrificed 120 hours after operation, reveals fibrinous coagulated clot protruding into open right bronchus. Cross-section of clot formation revealed. As this contracts, it is plain to see from this specimen why, and how, the centermost portion forms an elevated ridge with two lateral depressions as seen in B and C, both of which are healed bronchi in dogs sacrificed after more than four weeks. The suture in B, Dog R-11, was in the pleura; in C, Dog R-2, the elevated ridge has been contracted down by the fibrous tissue substitution; whereas in A, Dog R-30, this substitution has not yet taken place and, therefore, the fibrous clot protrudes further into the bronchus than it will eventually.

invariably protruded into the open end of the amputated bronchus, completely filling it; extending into the lumen for varying distances toward the trachea, it covered over the cut ends of the bronchus and blended with the peribronchial and subpleural connective tissue. At this stage, the lumen of the open end of the bronchial stump was always reduced somewhat in diameter and in some instances appeared conical in shape, in others more cylindrical. The microscopic sections corroborated the gross appearance, and showed the open cut end filled with a fibrinous coagulated mass which completely embraced the cut end of the bronchus (Fig. 20). Although the bronchus, like a blood vessel, when cut across attempts to close itself, the open end of the tube was reduced in diameter and appeared to be drawn into a cone-shape by contraction of the fibrinous plug. The fibrinous coagulated mass varied in

size, depending on the size of the open end of the bronchus. Microscopically, it consisted of coagulated fibrin in the meshes of which were many polymorphonuclear leukocytes, small lymphocytes, and red blood cells.

Further study showed that as one proceeded from the innermost protruding portion of the fibrinous plug peripherally to the overlying pleura the

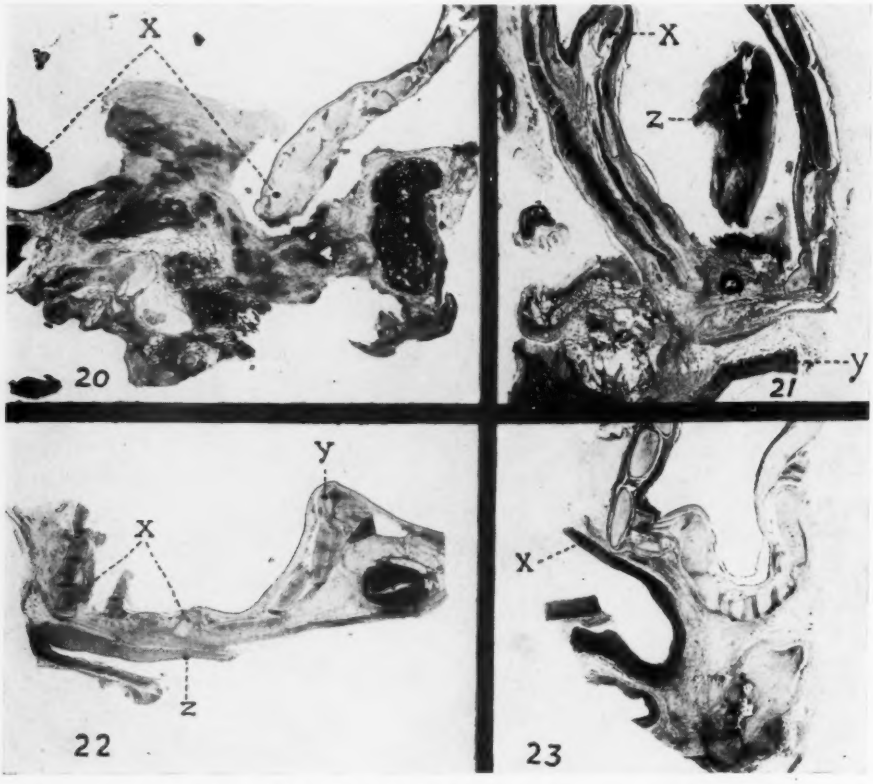

FIG. 20.—Dog X (8 micra, x4): Dog sacrificed after 48 hours. Note ends of bronchus at X, in which the entire opening is plugged by a mushroom-shaped coagulated mass. Red blood cells shown as dark areas in meshes of fibrin. Ends of bronchus embraced by coagulated mass.

FIG. 21.—R-30 (8 micra, x5): Photomicrograph of gross specimen shown in Fig. 19. A. Note coagulated mass protruding in bronchus plugging the open end, Z. Carina of trachea is shown at X; mediastinal pleura at Y. This represents the healing of the bronchus at 120 hours.

FIG. 22.—Dog R-29 (8 micra, x6): Dog sacrificed after two weeks. Lebt bronchus shows contracting mass of granulation tissue with remaining coagulated fibrous clot still protruding into bronchus. Fibrous tissue has grown into this mass from peribronchial and submucosal tissue. Mediastinal pleura shown at X; carina at Y; and ends of bronchus at Z.

FIG. 23.—Dog R-18 (8 micra, x4½): Dog sacrificed after four weeks. Although no sutures were used in the closure of this bronchus, inturned cartilaginous rings at the cut end of the stump have been drawn completely across the lumen of the bronchus into apposition with each other by the contracting fibrous tissue formed about this open end. Mediastinal pleura shown at X.

microscopic appearance changed. The innermost portion was predominantly coagulated fibrin, the cellular infiltration increasing as the base of the clot was approached. Further, the fibrinous mass seemed to blend with the peribronchial submucous connective tissue, as well as with the overlying subpleural areolar tissue. Often hypertrophic lymph follicles, with conspicuous

germinal centers, made up part of this tissue mass. The entire mass was covered over with the mediastinal pleura. As if to emphasize the pull or contraction of the coagulated fibrin, the epithelial lining and submucosa of the cut end would often be drawn in towards the center of the lumen. In the specimens obtained from animals after 96 and 120 hours the fibrinous plug seemed to contract more and become more dense (Figs. 19 and 20). The extrabronchial base of the plug was beginning to be invaded by granulation tissue, preceded by invading fibroblasts and endothelial cells. This granulation tissue came from several sources: namely, the peribronchial connective tissue, that lying beneath the mucosa, and also the subpleural areolar tissue (Fig. 22). The cellular infiltration seemed to diminish and the fibrinous plug

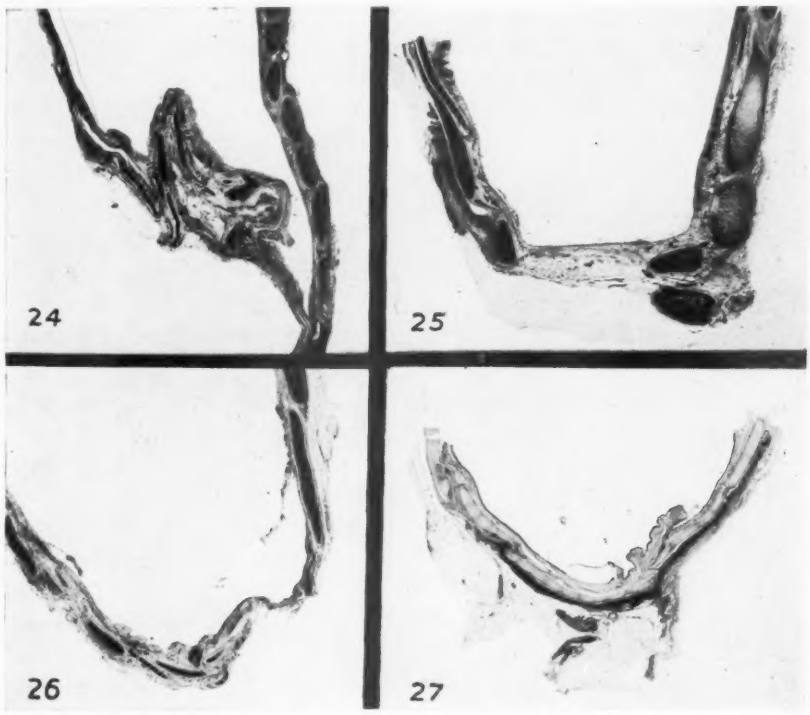

FIG. 24.—Dog R-5, (micra 8, x4½): Dog sacrificed after four weeks. Although no sutures employed to close open end of amputated stump, contracting fibrous tissue has not only drawn the walls of the cut end of the bronchus together, but actually inverted them. Epithelium has grown over this papillomatous infolding. This type of healing explains the irregular internal surface of these stumps and why there is a central ridge with two lateral recesses as one looks down the inside of the bronchus.

FIG. 25.—Dog R-6 (micra 8, x6): Dog sacrificed after four weeks. Cut end of bronchial stump healed over by thin membrane derived from bronchial and subpleural connective tissue. Cut cartilaginous rings have been angulated by the contraction of the fibrous tissue.

FIG. 26.—Dog R-1 (micra 8, x6): Healed stump of bronchus by thin membrane derived from peribronchial and subpleural fibrous tissue; slight tapering of cut cartilaginous rings in end of stump. No atrophy of this terminal cartilage.

FIG. 27.—Dog R-19 (micra 8, x6): Dog sacrificed after four weeks. Right bronchus, terminal cartilage pulled completely across open end of bronchus. Although no sutures whatever used in the closure, these cartilages were pulled into this position by contracting fibrous tissue. The remains of the coagulated fibrinous clot may be seen in the papillomatous fibrous mass still protruding into the upper blind end of the healed stump.

protruding into the bronchial lumen had begun to retract. The granulation tissue contributed by the peribronchial connective tissue appeared to sweep around the cut ends of the cartilagenous rings, joining with that contributed by the submucosal layer and eventually connecting with the granulation tissue in the center of the lumen or the fibrinous plug. The central portion seemed to spring largely from the subpleural areolar tissue. In some specimens, at the end of 96 hours, the pull resulting from the gradual condensation and contraction of this granulation tissue would not only approximate the cut ends of the bronchus (Fig. 23), but in some these edges were actually inverted into the bronchial lumen (Fig. 24). In others there was only slight angulation of the cut ends of the bronchus, the granulation tissue forming just a thin occluding membrane across the cylindrical end of the tube (Figs. 25 and 26). There were all variations between these extremes. Complete regeneration of the columnar bronchial epithelium and the underlying mucous glands did not occur. Thus, the amount of regeneration in proportion to the internal lining epithelium varied in individual animals. Bronchial epithelium is fairly prolific and the early 72- to 120-hour specimens, as well as those some months old, demonstrated the way in which a thin sheet would grow into all the irregularities and crevices on the internal surface of the protruding, contracted granulation tissue plug. In cross-section, both gross and microscopic, the internal surface was often irregular due to papilloma-like infoldings or bands or both, apparent on the healed inside surface of the bronchial stump (Fig. 27). There was never any evidence of regeneration of cartilage. In those instances in which the bronchial walls were approximated by the pull and contraction of the granulation tissue, the cut ends of the cartilaginous ring were, as stated above, either in apposition or infolded or again just slightly angulated. After a few months the specimens revealed that these bits of cartilage became atrophic, staining a slight pink with eosin, and forming part and parcel of the fibrous tissue plug that closed off the end of the bronchus. Microscopic sections of the specimens of the completely healed bronchial stumps, examined some months after the original operation, showed a further progression of the healing processes described. The vascular granulation tissue was transformed into white fibrous connective tissue so that the hitherto coagulated fibrinous plug passed through the stage of granulation tissue to fibrous connective tissue. The final form of the closed or healed stump was pleomorphic, varying somewhat in each animal.

Discussion of the Experimental Results.—In the first series of experimental animals it was shown definitely that only in a small percentage of instances had the amputated bronchus healed as sewed at the time of operation. In the largest percentage the healing of the bronchus showed variation in healing; part might be healed as sewed at operation, while the remainder would be wide open and healed over by either a fibrous tissue plug protruding up into the open end of the bronchus, or a fibrous tissue sheet which apparently developed mainly from the nonserous surface of the mediastinal pleura. Regardless of the method in which stitches were placed, whether as inter-

rupted or interrupted mattress sutures, a high percentage of these would cut through the bronchial wall and allow the walls of the cut end of the primary bronchus to separate, either in part or throughout the entire width of the bronchus. The healing would then take place by the sealing off of the open end due to an overgrowth of fibrous tissue from the peribronchial and nonserous surface of the mediastinal pleura. If the latter structure was sewed over the end of the bronchus at the time of operation, complete healing occurred in the manner described in the first series of animals in which mattress sutures were employed. If, on the other hand, as demonstrated in a number of previous series, the mediastinal pleura was not sutured over the end of the bronchus, a certain percentage would leak, regardless of the type of suture or the manner of its insertion; and as is well known, if the bronchus does open between the first and second week, the result is usually fatal in experimental animals.

From this second series of 48 dogs, it may be concluded that the bronchi have healed as completely as those in which sutures were used. There were no infected stitch abscesses in the proximity of the healing cut ends of the bronchi that might eventually have caused a more extensive suppuration; hence, in this respect the tissue repair was more perfect in this series than when sutures were used. Furthermore, the morphologic and microscopic appearance of the healed bronchial stumps presented the same degree of variation observed when sutures were used to close the bronchi. It would seem that the tissue which brought about the final closure of the open end of the bronchus must be considered as being derived mainly from the bronchial walls.

As has been pointed out, the manner in which this closure takes place varies widely. One extreme, in which the cut ends or walls of the bronchus are mechanically pulled, so to speak, towards the middle of the lumen by contracting scar tissue, results in an inturned or even inverted cuff. In this type the healing by granulation is minimal and the original bronchial walls have actually occluded the open end. Thus the tissues bringing about occlusion of the bronchus are almost entirely derived from the bronchial walls. In those instances in which the open end is closed by granulation tissue alone, it is fully apparent in the microscopic sections that the fibrous tissue is derived, at least largely, if not principally, from the peribronchial connective tissue, as well as from the submucosa. A definite contribution from the subpleural areolar tissue is added. Epithelial lining grows in from the bronchial epithelium, but there is no apparent new growth of cartilage. In this latter type of healing it is obvious, therefore, that the bronchial walls also contribute largely to the formation of the tissues which occlude the open end of the bronchus.

It may be stated definitely that in the second series of 48 experimental pneumonectomies, healing of the bronchus took place entirely at the cut end, as no sutures were employed. It may also be said and quite as definitely that in the first series of 36 animals in which the bronchus was closed by inter-

rupted mattress sutures, the healing in the great majority; namely, 82 per cent, of the animals occurred at the open cut end of the bronchus and not along the suture line. It would, therefore, seem reasonable to conclude from our experimental observations that the vital point of healing of the amputated bronchial stump is at the cut end and is not related, in the majority of instances, to the use of occluding sutures.

REVIEW OF THE LITERATURE

The earliest experimental work on resection of the lungs was reported by Glück,[1] in 1881, when he removed the entire lung on one side from six dogs and 14 rabbits. With the exception of two rabbits, all died in from seven to ten days. In some of the rabbits pericarditis and septic pleuritis developed between the 7th and the 10th postoperative day. The operations were performed with aseptic precautions. It would seem likely that some infection from within as well as from probable opening of the bronchus was responsible for the death of Glück's animals.

Block[2] also performed experiments in 1881, with equally discouraging results. He extirpated the lung in five rabbits and four dogs. In only one instance was he able to keep an animal alive more than 14 days. The rabbits died, for the most part, immediately after operation. The dogs lived longer, some even to the 14th day. Unquestionably, sepsis was the cause of death in the animals which did not die from the operation. Four animals subjected to operation one month after the original experiments died of fibrinous hemorrhagic pleuritis.

Biondi,[3] in 1884, reported his results, which were the best of those of the early experimenters. An attempt was made to produce a localized pulmonary tuberculosis by means of the injection of tubercle bacilli into the lung. About 25 to 30 days after the initial injection of tubercle bacilli the animals were operated upon and the lung was resected. The experimental animals consisted of five dogs, six cats, and ten rabbits. About half the total number died of septic pleuritis or pericarditis after the initial injection. Four animals died immediately after extirpation of the lung, with seven surviving. In nine animals pleuritis developed following extirpation of the lung.

Willard,[4] in 1891, performed a successful pneumonectomy in a dog by suturing the stump, which he ligated *en masse* into the wound. In 1889, Murphy[5] lost eight of nine dogs with septic pleuritis. In 1907, Tiegel,[6] and Mitt,[6] advocated the use of a loose silk ligature placed about the hilum, to be followed by peripheral ligation of the vessels to that portion of the lung to be resected. The bronchial stump was cauterized and ligated distal to the first mass ligature. This method, as would be expected, was followed by hemorrhage and bronchial fistula. Frederick,[7] in 1908, advocated separate ligation of the hilar structures and removal of the mucous membrane from the bronchus to such an extent that the denuded bronchial wall could be approximated and ligated.

Danielson,[8] in 1908, suggested the use of silk to close the main bronchus.

Robinson,[9] also in 1908, performed thoracotomy upon 30 dogs under positive pressure anesthesia. In 12 of the animals pleurotomy was performed without interference with the lung. In 15 animals operated upon, part of or an entire lobe was resected, one with removal of two entire lobes and one with removal of the entire lung. There were five deaths from sepsis, one case of sepsis being due to leakage from the bronchial stump. There were four additional cases of infection, due to localized empyema or parietal wound infection; the animals, however, recovered.

In 1909, Halsted [10] performed 21 consecutive thoracotomies in which there was only one primary infection of the thoracic cavity. These results contrasted strikingly with the earlier results, marking what might be called the advent of aseptic surgery applied to the thorax. Halsted, assisted by Willis D. Gatch, concerned himself chiefly with the bronchi and the vessels at the root of the lungs and various lobes. Occlusion of the main, and of the primary and secondary divisions of the bronchus was practiced, various methods and almost all degrees of occlusion being tested. The lung was only occasionally excised. Bronchial occlusion was secured by ligations with metal bands. In no instance were the experimenters able to crush the bronchial wall with the encircling bands, and in no instance did these bands give rise to pulmonary emphysema or dilatation of the bronchus. The bronchus could not be obliterated by bands. They also found that ligatures of black silk did not completely occlude the bronchus or permanently obliterate it unless the mucosa was crushed. Permanent obliteration was accomplished following bisection of the bronchus, careful excision with the scalpel of its mucosa, and approximation of the raw surfaces by running sutures of fine black silk. By this method the bronchus could be converted into a solid fibrous cord. Halsted gave up the inversion of the bronchus because it seemed too short for nice adjustment.

In this article Halsted did not refer to the use of mattress sutures nor did he state whether the sutures were put in the end of the bronchus or through the bronchial wall proximal to the cut end. We have repeated his observations, employing mattress sutures, and have found the closure to be very satisfactory in the dog and also in the human being. Halsted's experiments represent, up to that time, the most fundamental contribution to the surgery of the lung, particularly with regard to the closure of the primary bronchus.

Willy Meyer,[11] in 1909, described an inversion method in which the bronchial mucosa was undisturbed. In 21 extirpations there were four deaths due to sepsis and to leakage from the bronchial stump. The main bronchus was crushed and ligated. The method of Willy Meyer is undoubtedly a very satisfactory one for experimental pneumonectomy, although unnecessary in the light of our present experience; but this method is a typical example of one described many times since in the literature, which is totally inapplicable to human beings, mainly because of the stiffness and rigidity of the bronchi.

Robinson and Sauerbruch,[12] in 1909, reported 38 total extirpations of

the lung in which there were four recoveries. Their report of other experimental results included those of von Haecker. They claimed that five animals died from sepsis and 11 from leakage from the bronchial stump, and that in 18 there was a transudation into the pleural cavity upon the operated side, followed by death. This was more than likely a septic pleuritis.

Quinby and Morse,[13] in 1911, in their series of experiments, pointed out, for the first time, the importance of peribronchial tissue and its use in the closure of the bronchus, and called attention to the fact that they were never able to secure an air-tight closure of a bronchus which had been thoroughly isolated before tying. They further suggested, in accordance with the point brought out by Tiegel, that bronchial wounds heal best when the stitches are placed only in the peribronchial tissues. They also stated that inversion of the primary bronchus on the right side, before the departure of the branch to the upper lobe, is impossible because it is too short. Quinby and Morse called attention, for the first time, to the advantage of employing a lappet of lung which is opposed by a stitch to the hilus denuded of pleura because as they said, "as is well known the lung has adhesive and walling-off power quite like the omentum," and they recalled the adhesions of the lung to an esophageal suture in previous experimental work. They also described, completely, the intrathoracic restitutional mechanism by which, following total pneumonectomy, the vacant thoracic cavity is filled up by the heart and the contralateral lung moving over toward the operated side. "The diaphragm rises and the ribs flatten with their interspaces shortened." Overinflation of the lung as the thoracic cavity is closed was recommended. Another valuable suggestion that these authors made is painting with tincture of iodine the region of the lung root after it has been carefully dried and the toilet of the wound completed. This is the first time this important step had been mentioned.

Quinby and Morse operated upon 38 dogs, 30 of which recovered and eight died. The right lung was excised in 17, with three deaths, the left in 21, with five deaths. There was no mortality in the last nine cases. Unquestionably, Quinby and Morse's contributions to thoracic surgery must be considered among the most fundamental, and would seem to have been insufficiently emphasized in the literature.

In 1912 Garré[14] advocated sewing a piece of lung tissue over the open bronchus after having placed a ligature about the latter structure. This method has been suggested independently, in recent years, by Churchill.

Henschen,[15] in 1914, proposed the introduction of a roll or plug of fascia into the lumen of the divided bronchus, the stump being closed over it. This procedure was later carried out by Halsted and Crowe. Giertz,[16] also in 1914, used fascia to close the bronchial stump by suturing it over the end of the bronchus and using silk stitches to hold the fascia in place. The bronchus was first closed with mattress sutures of silk and then covered by the fascia which was sutured to the peribronchial tissue. This method was similar to but not exactly like the one advocated more recently by Taffel in 1940.

Giertz operated upon 10 dogs and lost two of them. In 1914, Kawamura[17] reported his observations on experimental pneumonectomy, having operated upon 23 animals; three died of sepsis, two deaths being secondary to leakage from the bronchial stump.

Heuer and Dunn,[18] in 1920, reported their results on experimental pneumonectomy in which they employed all the different methods of suturing the bronchus that had been used before that time. Their results confirmed many of the previous observations made by Quinby, and also by Kawamura, in regard to the fate of the intrapleural cavity resulting after removal of the lung and the methods for its obliteration, as well as the reactions on the part of the remaining lung to the presence of simple dilatation of the definitive respiratory unit; namely, the ductus alveolaris, the atria, and the alveoli, instead of an hypertrophy and hyperplasia of the lung parenchyma. In 23 dogs in which total pneumonectomy was practiced there were 13 recoveries and 10 deaths, the fatalities occurring from four days to two months after operation. Six of the deaths were due to epidemics of distemper. The postmortem examinations in this group did not show a single instance of infection of the parietal wound or pleura or leakage from the bronchial stump. One animal died of a simple pneumonia, unassociated with other evidences of distemper. One animal died from starvation two months after operation. Two animals died of acute pneumothorax, the result of leakage from the bronchial stump, and in one of these the failure to secure adequate closure of the bronchial stump was intentional. One died of necrosis of the bronchial wall following application of a flattened metal band. In eight animals the bronchus was crushed and transfixed by a single ligature of heavy EE silk, and it is stated that in none of these animals did the bronchial stump leak, nor was there any pleural infection, all having lived more than one month following operation. The size and age of the dogs so operated upon was not stated. This point is brought up because it is a well known fact that in younger dogs and puppies, as well as in children, simple ligature is often efficacious, whereas it is not so in older and larger dogs and in adult human beings. It is also interesting to note that in five of the dogs, so operated upon by Heuer and Dunn, the bronchial stump had retracted into the mediastinum and was covered by mediastinal pleura, although this had not been sewed over the stump at the time of operation.

It is interesting to note that the illustrations of the healing of the bronchus, in the gross, show that exactly the same type of healing occurred in the bronchi which were ligated that we, in our series, found to occur in the end of the bronchi in which no ligature or stitches were placed, the mediastinal pleura having been merely drawn over the open end. I refer particularly to Figs. 4 and 5 in Heuer and Dunn's article. This fact would seem to suggest that, in their series, the ligated bronchi had become spontaneously covered with mediastinal pleura and had healed as did those in our series that were intentionally covered with serous membrane, the ligature probably having cut through and allowed the walls of the bronchus to open

up, as shown in their illustrations. If the ligation had held, the bronchial stump should have remained conical as left at operation. In illustration 3A, however, the end of the healed bronchus is of the same diameter as the lumen of the proximal portion of the stump. Figure 3A, especially, looks as if the walls of the bronchus had completely opened and subsequently healed by a fibrinous plug in the cut end.

The microscopic sections are even more suggestive of healing in the manner of those of our second series, in which no stitches were placed in the wall of the bronchus. In their Figure 6 the mesial section is again similar to our experiments in which no attempt was made to close the bronchus. In other words, the bronchial stump is healed with a fibrous plug; and if a conclusion can be reached from the study of photographs, it would seem likely that a number of bronchi in Heuer and Dunn's series had opened by being cut through by their ligatures or sutures and had healed in the manner described in our second series. Their illustrations, both gross and microscopic, showing the methods of healing following the use of different types of ligatures and sutures in closing the bronchus, are exactly similar to our illustrations in which the bronchus healed without any sutures or ligatures.

As one reviews the sections of the healing of the bronchial stump in the article by Heuer and Dunn, it would seem probable that their excellent results were obtained, as were ours, by healing of the bronchus through a fibrous or fibrinous granulation plug rather than from apposition of the walls by any particular method of suture.

We are particularly interested in Heuer and Dunn's report because in our first series of animals we also were of the opinion that the method of suture employed had a great deal to do with the type of healing. We soon discovered, however, from the gross and microscopic appearance of the healed bronchial stumps, that our results were exactly similar in every respect to those of Heuer and Dunn; and, except for the fact that they intentionally employed for closure two methods which they were sure would end fatally, their results were as favorable as ours. Heuer was the first to demonstrate the microscopic appearance of healed bronchial stumps and also to point out that similar results were obtained following a variety of methods of closure.

In 1924, Bettman[19] reported his experiment in which he performed lobectomy, pneumonectomy, and isolation of the entire lung in dogs. He stated at the beginning of his paper: "After a protracted study of the subject and after numerous experiments, it must be admitted that we have not been able to close the large bronchi with any certainty of success by any of the methods reported. We have arrived at conclusions diametrically opposed to those of Heuer. According to our experiments, an isolated large bronchus will not heal. Smaller bronchi can be sealed, but the tissues which close them are not derived from the bronchi themselves, but from the peribronchial structures. In short, following pneumonectomy, our dogs almost inva-

riably (there were two exceptions) died. Following simple lobectomy the dogs almost always lived. In the group in which lobectomy was done the secondary bronchus of the lobe was closed with a simple ligature of No. 2 catgut, and, at autopsy, it was found that the visceral pleura of the adjacent lobes was glued over the amputated bronchial stump by adhesions. On microscopic examination the sections showing the healed bronchi revealed that the occluded end was blunt rather than conical." This indicated to us that the ligature had given way and the bronchus, opened up, subsequently, healing, as in our series, in juxtaposition to the pleura. Bettman states: "In the majority of our sections the remaining lung was plastered over the cut end of the bronchus and it was apparently this reaction which had saved the bronchus from reopening. The fibrous tissue which had closed the bronchus seems to have sprung from the visceral pleura firmly holding this pleural cap over the cut end."

Bettman's illustrations, both camera lucida diagrams and photomicrographs, are similar in every respect to ours. He mentions cysts lined with epithelium which appeared in the blunt occluded end distal to the closure of the lumen of the secondary and tertiary bronchi. These cysts were assumed by Bettman to be due to infolding of portions of the lumen of the bronchus by the ligature, but he thought that these cysts reduced the strength of the occlusion of the bronchus. This has been found by us not to be true. The cysts, as we have pointed out, are due entirely to the preservation of live epithelium distal to the ligature or suture line of the bronchus regardless of whether it is a primary, a secondary, or a tertiary bronchus. Also, we feel that Bettman considered the bronchial wall inert. We agree with this observation from the standpoint of regeneration of cartilage, but in no other respect. The peribronchial connective tissue together with bronchial smooth muscle, muscularis mucosae, and the fibrous tissue springing therefrom, as well as the mucosa, contributes always to the closure of the end of the bronchus. In one instance Bettman mentions a lobectomy of the right lung in which the bronchus was ligated and on healing . . . "there was a very fine membrane of connective tissue which stretched across the bronchus much as a thin piece of rubber might be stretched over the end of a metal tube. Any slight increase in pressure undoubtedly would have torn open the bronchus." . . . This assumption, of course, was found by our differential pressure readings to be far from the actual case. This thin membrane of connective tissue which Bettman refers to is an ideal form of healing in closure of the bronchus.

In Bettman's series of 26 dogs, in which the *total lung* had been removed, all except one died within the first week. After reviewing Bettman's experiments, the only explanation that we can make is that in those in which catgut was used as the suture material, the catgut probably gave way. Cauterization of the stump of the bronchus and crushing it probably also played their part, because autopsy revealed that the stumps, whether inverted by silk or by catgut, opened. This result must have been due to necrosis of the tissue in

which the stitch was taken as a result of crushing and cauterization. If we may interpret experiments from a previous author's work, it would be our opinion that if these stumps, in spite of the fact that they were crushed and cauterized, had been covered with mediastinal pleura or pleuralized, in all probability, a high percentage of them would have successfully healed and the dogs would have survived.

It would seem to us that Bettman's series is sufficient evidence that catgut should not be used, and also that any trauma, such as thermal or chemical cauterization or mechanical crushing, should be carefully avoided.

In a later contribution Bettman, *et al.*,[21] in 1928, reported another experiment which supported the impression that we obtained from Bettman's first report; namely, that necrosis of the cut end of the bronchial stump and the tissues surrounding it will prevent primary healing of the bronchus and thus allow ligatures in this region either to cut through or to pull out. Such necrosis will also prevent successful *per primam* agglutination of the amputated bronchial stump to opposing structures such as overlying pleura. Their reports show that in a series of six dogs, in which there was massive ligation and crushing of the stump previous to the lobectomy (not pneumonectomy), four of the animals died of reopening of the bronchial stump, whereas in seven dogs in which the vessels were individually ligated, without trauma from crushing or cauterization, only one died from some cause other than opening of the bronchial wound. These observers performed only one total pneumonectomy and the method of closure of the bronchus was not given, but it is to be assumed from their report that it was probably ligated with catgut. This dog died on the 6th day from reopening of the bronchus, and the authors came to this conclusion: "We did not feel justified in sacrificing any more animals to prove that the bronchial stump fails to remain closed following pneumonectomy in contradistinction to lobectomies."

It is unfortunate that Bettman and his coworkers did not apply their lobectomy technic to pneumonectomy; in other words, that they did not cover the amputated bronchial stump, for their observations in the healing of the secondary and tertiary bronchi following lobectomy are similar in all respects to our observations following total pneumonectomy.

Feiermann,[20] in 1925, reviewed various methods of closing the bronchial stump, and concluded that the method to be preferred was that suggested by Willy Meyer. Up to that time, however, previous authors had had just as successful healing with other methods of closure as with that advocated by Meyer.

Joannides,[22] in 1928, suggested leaving a portion of the lung tissue or a lobe in contact with the amputated bronchial stump; in other words, cutting through a portion of lung tissue. This procedure is impractical and obviously would prevent one from doing a total pneumonectomy. It is, therefore, an argument that, in our opinion, is not pertinent.

Schleuter and Weidlein,[23] in 1928, suggested invagination of the bronchus by cutting the primary and secondary bronchi between ligatures and then

inverting each with a purse-string suture of No. 1 chromic catgut and, in the case of the primary bronchus, reinforcing it by three mattress sutures of silk. By this method the author performed four total pneumonectomies, following which one animal died of empyema on the fourth day. The objection to this method is the same as to the method of Willy Meyer, in that it is not practical and applicable to the human being, nor is it necessary for a successful closure of the primary bronchus in the animal.

Nisson,[24] in 1931, suggested ligature *en masse* as a two-stage procedure, surrounding the lobe to be excised with a coarse silk-mesh bag to obliterate the pleural cavity, followed by amputation two to four weeks later. This method may have some application in suppurative cases, but would, it seems to us, prove inefficacious when dealing with malignancy.

Adams,[25] in 1931, attempted to produce bronchial stenosis by the use of 35 per cent silver nitrate injected intrabronchially prior to operation. This procedure would seem ideal but was not successful in our hands, except in one case in the human being in which there was a small opening in the bronchus *following* amputation of the lung. This method of Adams' was successfully used in experimental closure, but we believe that the human bronchus is too rigid to be stenosed in this manner.

In animal experimentation Blalock,[26] in 1933, found the method of Adams to be associated with a rather high mortality due to inflammatory sequelae following the application of the silver nitrate to the bronchial wall.

Longacre,[27] in 1935, using a method of inversion of the bronchus, operated upon a series of 30 dogs and found, as have others, that silk ligatures were to be preferred to catgut; he showed that in Series (A), 12 dogs, in which chromic catgut was used, the mortality was 75 per cent, and the incidence of bronchial fistula 66.6 per cent, whereas in Series (B), 18 dogs, the mortality was 16.16 per cent, and the incidence of bronchial fistula 5.5 per cent, where the suture material employed was fine and medium silk.

It is interesting that in the experiments of Longacre,[27] in 1935, in which catgut was employed and the bronchus opened, he found the healed closure to be the same as in our series in which no sutures were placed in the cut end of the stump. He says: "The openings were sealed over with a loose network of newly formed granulation tissue. By the end of three or four weeks this had become more dense and the stump consequently more solid. By this time the external surface of the stump was pleuralized and the mucous membrane was starting to cover the inner surface of the bronchial stump."

It is interesting to note that Figure 9, in Longacre's report, showing the healing of the bronchial stumps demonstrated, as did Heuer's and ours, the same type of healing; yet the method of closure employed by Longacre was entirely different from those used by Heuer, and by us.

In 1937, Thomas *et al.*,[28] presented a technic for total pneumonectomy in animals in which they stated that two encircling sutures were placed about the lumen of the bronchus tight enough to occlude the lumen, but not tight enough to crush the bronchus or the peribronchial tissue. This procedure requires a

delicacy in tying which is not given to the average surgeon, for the resistance of the epithelium to the occluding ligature must be very difficult to appreciate. Peribronchial tissue was utilized by them to oversew the stump of the bronchus. In all, three layers of suture line were generally used, and the bronchial stump was pleuralized, much as the cervical stump is peritonealized following hysterectomy. Under "*Results*" they did not mention the number of dogs operated upon, but merely said that a "few" were lost. Under "*Cause of Death*" they stated that "for the few dogs that died after operation the average length of life was 7.3 days." They did not state how many dogs died. No mention is made of the method or type of healing as evidently the bronchial stumps were not examined postoperatively.

In 1940, Taffel[29] suggested closing the opening in the lower end of the trachea, following removal of the left primary bronchus, "with a stamp of deep thoracic fascia." He employed this method successfully in two dogs. The description of the microscopic findings and the illustrations of the healed bronchial stump (Fig. 10, Dog No. 426) again shows the same type of healing that we found to take place in our second series. The fascial grafts which Taffel used had disappeared after 8 and 12 weeks, when the dogs were sacrificed. As Taffel suggests: "The graft did not appear to remain viable but acted as a temporary and airtight scaffold." As in our series, the bronchus in these two instances was held together by granulation tissue. The cut cartilaginous rings are almost approximated by the pull of the contracting fibrous tissue, as shown in Figure 10 of Taffel's article. Taffel's suggestion is a very ingenious one which will undoubtedly prove to be useful in certain cases of pneumonectomy in man.

Stafford,[30] in 1941, reported a plastic closure of the bronchus in a series of 33 dogs, in which three died because of technical difficulties and three from tracheal fistula. Stafford also covered the operative field with mediastinal pleura, simply with the idea of covering over a denuded area. No data or description of the microscopic appearance of the healing of the amputated bronchial stumps are given. However, it is unlikely that such a method, in which flaps of the bronchial wall are to be used in order to close the open end of the amputated bronchus, would be applicable to the human being. Other than the anatomic differences between the primary bronchus of the dog and the human being; that is, the increased rigidity of the human bronchus, there is also the fact that the primary bronchus is usually involved in the growth for which the lung is to be removed. There is, therefore, not enough of the bronchial wall remaining from which to select and cut a flap.

Thus, it would appear that in the majority of instances of experimental pneumonectomy the bronchial stump healed in the same manner regardless of the type of closure employed, whether sutured or ligated or whether any closure was attempted at all, provided the end of the amputated stump had been pleuralized, either intentionally or spontaneously. This fact would

seem to nullify the influence of any particular type or method of suture upon the manner in which the healing of the bronchial stump occurred.

CLINICAL OBSERVATIONS

Clinical observations on the closure of the human primary bronchus in a series of 61 consecutive total pneumonectomies, extending over a period of nine years (since 1933), have emphasized the fact that to obtain the optimal healing of this structure, certain procedures in the closure must be observed. In the early cases of this series various methods were employed to close the bronchial stump, primarily because the clinical data on this subject were extremely meager, and, secondarily, because suggested procedures emanating from experimental pneumonectomy were not applicable to the human being. It was, therefore, concluded that closure of the primary bronchus in the human being was an individual problem due mainly to anatomic differences from other species, which could not be worked out in the laboratory but must be solved in the operating room. Thus, many different methods of closing the human bronchus were resorted to, which employed both absorbable and nonabsorbable suture material applied in various ways. It was early recognized that absorbable sutures were too frequently unreliable and this type of suture was soon given up. Circumferential ligatures of fascia, braided silk, different wires, and bands were discarded because it was found that they would cut through the bronchus. In 1939, the employment of a primary encircling ligature about the bronchus was suggested in addition to the use of mattress sutures to close the end of the stump. Although this method was the most successful employed in this series of cases up to that time, in many instances the closure was unsatisfactory. In four cases the circumferential ligature was coughed up after the patients had been discharged from the hospital for some months. In others, there was reopening of the stump to a greater or less degree. The majority of these patients lived, and fortunately a localized area of suppuration was walled off which drained for months, but eventually healed. In three, it was necessary to perform a posterior thoracoplasty to bring about closure of the chronic empyema cavity and of the bronchus.

The success or failure of the closure depended on unknown factors aiding or interfering with complete healing. Why, with the same technic of closure, would the majority heal solidly while a minority opened to some degree? Of the 61 patients upon who total pneumonectomy was performed, 47 (77.1 per cent)lived. In 34 of these (72.3 per cent) the bronchus healed without leaking. An opening occurred in 13 (27.7 per cent) who survived and, excepting the three upon whom a posterior thoracoplasty was performed, the bronchial fistula, in all, eventually closed spontaneously. Autopsy on the 14 (22.9 per cent) patients who died in the hospital revealed that in three the bronchus had opened wide within the first week. Two of these closures were made with catgut and were early cases in the series, but one was a recent case closed with silk sutures. This patient's

case was of particular interest and will be discussed later in this paper. Absorbable sutures are no longer employed as they are now considered unsafe. Nevertheless, with the first 30 patients there was increasing apprehension concerning the clinical postoperative course during the second week. It has been usually about the tenth to the fourteenth postoperative day that, beginning with an elevation of temperature and pulse rate, progressive and unmistakable signs of bronchial leakage have occurred in these unfortunate patients. Including the three patients who succumbed as a result of opening of the bronchus, together with the 13 who survived partial opening; that is to say, 16 cases out of a total of 61 complete pneumonectomies, the closure of the primary bronchus was insecure or failed to heal solidly in a startlingly high percentage of cases (26.2 per cent).

At a loss to correct our faults following a critical analysis of all the experimental and clinical data available, we decided to take the problem to the laboratory in order to determine the mechanism by which and the manner in which the bronchus would heal; and at the same time to determine a method which would prove to be satisfactory in the experimental animal and applicable as well to man. The experimental data have been presented in the first part of this paper.

In addition to the experimental observations, however, the opportunity presented itself on six occasions to study the method of healing in the human bronchus from autopsy specimens. Autopsies were obtained on six patients who had survived total pneumonectomy for varying lengths of time and in whom the cause of death was unrelated to the operation. From the clinical standpoint, the bronchi had healed solidly in each case, and this impression was confirmed at autopsy by increasing the intratracheal pressure sufficiently to hyperexpand the opposite lung without producing demonstrable leakage from the closed bronchial stump. As in the experimental animals, the operated side was filled with water in order to facilitate the detection of bronchial leakage by the appearance of bubbles. In each instance the bronchus had healed completely and there was no leakage. When microscopic sections of these healed stumps were examined, however, it was noted that the manner and method of healing varied somewhat in the different individuals but followed exactly along the lines of our experimental observations. In not a single instance had the bronchi healed as sewed at operation, because in each case the ligatures or sutures or both had cut through and had either been coughed up or had remained encysted outside of the bronchial wall. As in the experimental closure the open end of the bronchus had healed by becoming filled with a fibrous tissue plug derived from the peribronchial, submucosal, and subpleural areolar tissue. In one, the walls of the bronchus had actually become inverted by the pull of the contracting granulation tissue. All of the healed stumps were more of the cylindrical than of the conical type. In the first patient death occurred two days after total left pneumonectomy, as a result of a plugging of the mitral orifice by a pedunculated fibromyxoma of the wall of the left auricle. In the

FIG. 28.—Autopsy CHI, (micra 10, x4½): Shows walls of bronchus at X; organizing granulating tissue plug at Y, occluding the bronchus; cutting silk sutures shown at Z; others probably discharged into lumen. Specimen two weeks postoperative.

FIG. 29.—Autopsy J.H.H., No. 14428 (micra 10, x4½): Death 19 days postoperative. Bronchus originally closed with interrupted mattress sutures. Cuff of open end of bronchus inverted by contracting fibrous tissue about the healed end of stump. Mediastinal pleura noted at X. Contribution of bronchial fibrous tissue observed at the ends of the cartilaginous ring approximating the ends of the bronchial stump.

microscopic sections the very early stages of the closure of the bronchial stump by a coagulated fibrinous clot was observed, which corresponded in all respects to our experimental findings. In this patient the bronchus had been closed with interrupted mattress sutures of silk, but the open cut end distal to the suture line was already undergoing the early stages of cicatrization due to the formation of surrounding granulation tissue.

The second patient in this series of autopsies died from a massive pul-

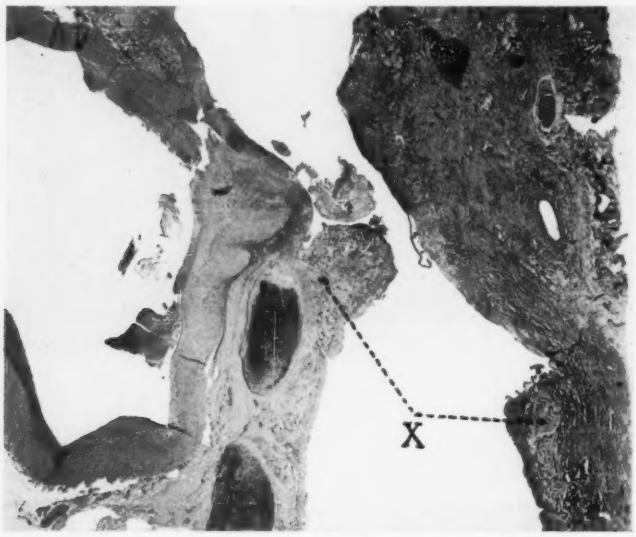

FIG. 30.—Autopsy J.H.H. No. 16923 (micra 10, x5): Bronchial walls, cut end of bronchus shown at X. Fibrous tissue mass plugging end of bronchus. Patient died one month following operation. Fibrous mass separated from one bronchial wall during cutting of section.

monary embolus 14 days after removal of the entire left lung. The microscopic sections of the bronchial stump (Fig. 28) showed the open end filled with granulation tissue over which epithelium had just begun to grow. Silk sutures which had cut through could be seen in the lumen and also outside of the bronchus. The bronchus in this case also had been closed with interrupted mattress sutures of silk; and although there was no clinical evidence of it, the silk sutures had already cut through by the end of two weeks, as demonstrated by the microscopic sections. Nineteen days after the right lung was removed another patient died of pulmonary infarction of the entire left lower lobe. A photomicrograph (Fig. 29) showed perfect infolding of the entire cut end of the bronchus. In this instance the amputated stump was also closed with interrupted mattress sutures of silk, leaving an open cuff of bronchus distal to the suture line. No attempt was made to invert the cut end of the bronchus. The silk sutures had cut through, but the open cut end had already healed sufficiently to prevent leakage. Thus, as in the experimental closure, each case seemed to heal in a slightly different manner as to the degree of participation of the bronchial walls by

infolding or inversion. In this instance the bronchial walls had been drawn together and inverted by the contracting granulation tissue so that only a small infolded area remained to be epithelialized. Following a low grade fibrinopurulent pericarditis which developed one month after total left pneumonectomy, the bronchus, although clinically solidly healed, as seen at autopsy, proved, by microscopic section, to have opened up into a cylindrical tube, the cut end of which was filled with a mass of fibrous granulation tissue (Fig. 30). Not one of the mattress sutures was in evidence although at least six had been inserted at the time of operation. The fifth patient in this series, who was operated upon in the fall of 1933, when her left lung was removed, returned six months later, and succumbed as a result of cerebral metastases. At the time of operation the bronchus had been closed with interrupted silk sutures near the cut end. The microscopic section is not shown because the original block that included the entire cylindrical healed end was cut across one side only. The remainder of the block was misplaced but part of the fibrous tissue plug could be observed. Only one small wall of the bronchus was included in the section, and although a badly planned section, the method of healing was obvious; that is to say, the open cut end had been sealed with fibrous tissue.

Following the now famous case of Evarts Graham, the first pneumonectomy performed in the Johns Hopkins Hospital was undertaken June, 1933, in a child three and a half years of age, for fibrosarcoma of the bronchus. The left primary bronchus was simply tied off with a braided silk ligature. The patient remained well, but unfortunately four and a half years later was drowned. The body was recovered and her father sent the thoracic viscera to us for study. Figure 31 is a photomicrograph of a section of the healed bronchial stump. It is obvious that the bronchus had been completely occluded by a fibrous plug of tissue. The remains of the silk ligature could be found in the fibrous mass of tissue surrounding the healed end.

It seemed, therefore, that the healing process of the primary bronchus in man was similar in every respect to that of the dog; that regardless of the type of sutures or ligatures employed to occlude the bronchus, they would, in the majority of cases, cut through the bronchial wall. If the sutures ulcerated toward the lumen they would be coughed up; but if they migrated towards the periphery they would be buried in the fibrous peribronchial tissue. Likewise, in man, as in the dog, healing of the bronchial stump took place, in the majority of cases, about the cut end of the bronchus some distance peripheral to the occluding suture line. The sutures or ligatures closed the bronchus temporarily, but could not be depended upon to maintain this occlusion for more than a week or ten days, during which time healing would occur at and about the cut end. The tissues that took part in the healing were derived mainly from the bronchial walls.

Discussion.—Based not only on experimental evidence, but also on observations on the healing of the primary bronchus in man, as determined

at autopsy, a method of closing the primary bronchus has been planned and employed in this series with far greater success than any used heretofore. In 27 consecutive patients in whom the bronchial stump has been so treated, there have been only two (7.4 per cent) in whom the bronchus opened. It is our opinion that the leakage in these two cases can be explained as due, not to the method of closure, but rather to an improper application of the method.

Based on previous clinical experience, together with our experimental

FIG. 31.—Autopsy J.H.H., No. 14937 (micra 10, x28): Fibrous tissue plug in end of bronchus completely organized, shown at X; bronchial walls at Y. Death 4½ years after operation, patient drowned.

evidence, the method of closure of the primary bronchus in the human being, which we feel offers the greatest opportunity of secure closure, is as follows:

The primary bronchus should be amputated near the bifurcation of the trachea, leaving only a short stump, so that this may be contained well within the mediastinum. The amputation should be executed with the scalpel in order that as little damage as possible is done to the cut end of the stump. Crushing or any form of cauterization, either thermal or chemical, should be strictly avoided because devitalized tissue must be sloughed off or replaced by viable fibrous tissue from the neighborhood. This process invites infection, ever present in the human bronchus to a greater or less degree. Also, primary agglutination of the vital amputated stump of the bronchus to the surrounding or overlying aerolar tissue thus would be prevented. Another reason why the bronchus should be amputated high and should be disturbed as little as possible in its areolar bed in the mediastinum is in order that the stump may be surrounded by vigorous granulation tissue

originating from the mediastinal areolar tissue and also from the undisturbed peribronchial tissue. The inferior thyroid artery gives off small branches to the lower end of the trachea and the first part of the primary bronchus. In some individuals the bronchial artery applies itself to the posterior aspect of the primary bronchus some distance from the bifurcation of the trachea, so that there may be a space between the areas supplied by the inferior thyroid

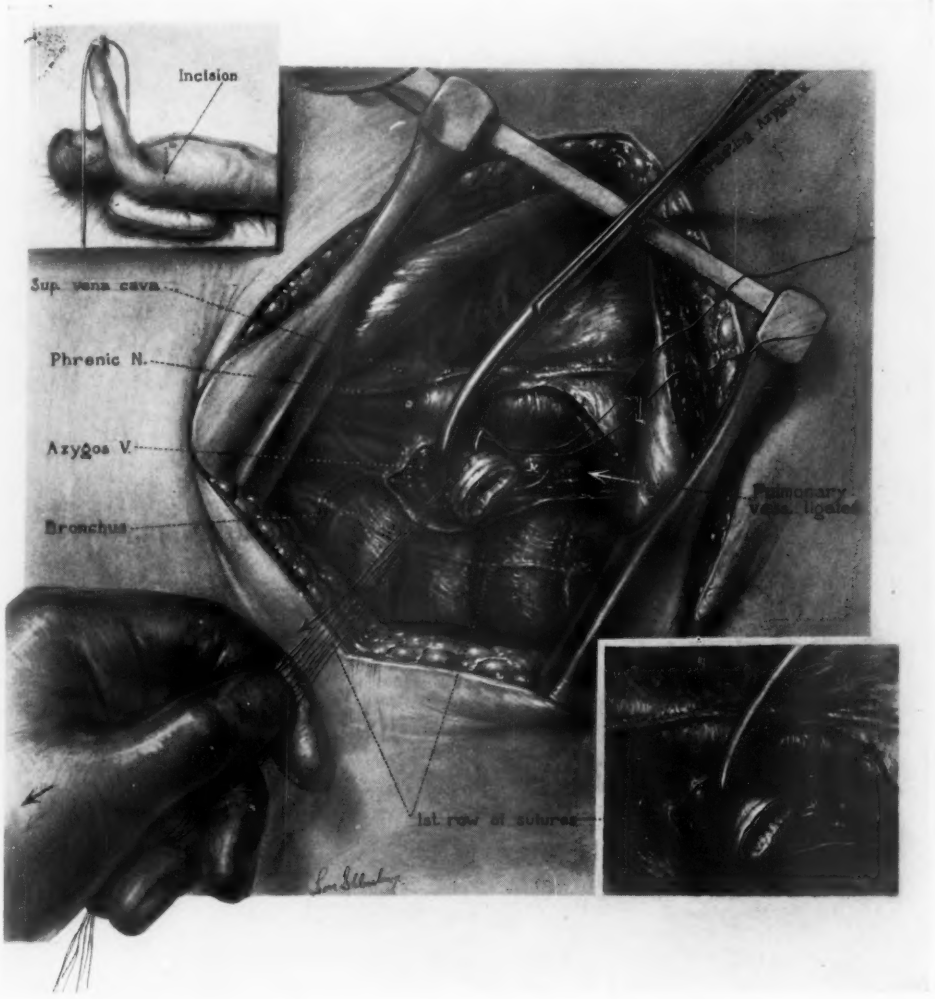

FIG. 32.—Shows position of patient on table, and anterolateral incision. Closure of right primary bronchus, mattress sutures, leaving viable cuff of bronchus distal to suture line. Insert, lower portion, shows sutured bronchus with viable open cuff residing in mediastinum.

arteries and the bronchial vessels that has a relatively poor circulation. The bronchus should not be dissected clean of its peribronchial areolar tissue, nor should the mucosa be disturbed in any way. As a rule, the bronchial artery should be ligated at the cut end and should not be occluded in one

of the mattress sutures. With a very thin cutting needle, mattress sutures of fine silk or cotton should be placed so that one leg of the suture passes around a cartilaginous ring (Fig. 32). The space between the legs of the mattress sutures should not be too narrow for fear of producing a slough from stangulation of tissue between them. The legs of the mattress may be

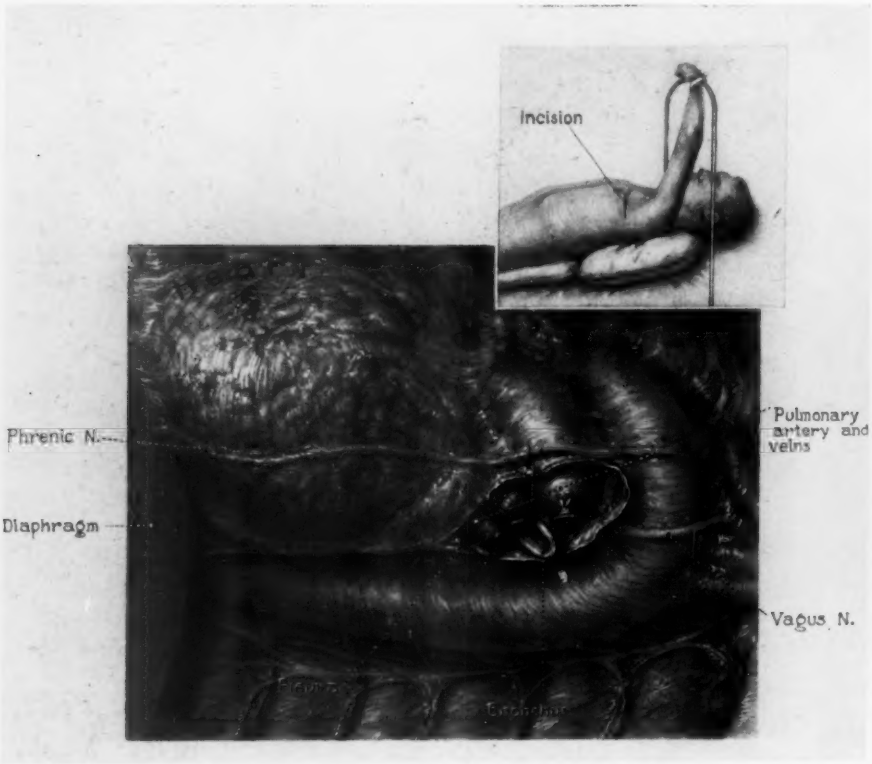

FIG. 33.—Shows relation of amputated stump which has been closed by mattress sutures high up near the bifurcation of trachea, open cuff of bronchus distal to suture line lying well within mediastinum.

roughly 4 or 5 Mm. apart, particularly in the posterior membranous portion. They are placed postero-anteriorly and then back again anteroposteriorly (Fig. 33). As a rule, six mattress sutures will suffice to close the bronchus completely. This closure should always be checked by filling the thoracic cavity with warm salt solution above the level of the closed bronchial stump and then increasing the intratracheal pressure. If the closure is not air-tight, bubbles will immediately appear.

As few sutures as possible should be used in order to preserve the circulation and thus the viability of the cut end. This cut end, not the area where the suture line is inserted, is the site of healing, and, therefore, constitutes the keystone to the arch of bronchial suture. The sutures are only used as a stop-gap to prevent air from blowing to-and-fro during respiration while

the all-important cut end is healing. The suture line in the bronchus should be placed as high up on the stump as possible, that is, near the bifurcation of the trachea. The reason for this is two-fold; if the sutures cut through or if they form localized areas of infection, these areas will be as far removed from the healing end of the stump as possible, and, secondly, when the

FIG. 34.—Denuded area containing hilar structures covered over by mediastinal pleura. Interrupted silk sutures closing lips of pleura except at either end. Four sutures, apart from those closing incision in the mediastinal pleura, hold nonserous surface of mediastinal pleura in apposition to cut end of bronchus.

sutures are placed near the trachea there is less likelihood of interfering with the bronchial artery. It is hazardous to place any form of suture in the cut end of the bronchus because no matter what the suture material, it constitutes an infected foreign body which will prevent primary agglutination and healing of the cut end. It has been shown experimentally and corroborated by human postoperative autopsy specimens, that the bronchus heals in the human being as its does in the dog; therefore, sutures, regardless of the method of insertion or type of material, will become infected and will cut. In the vast majority of instances the bronchus will not heal as it was sewed at operation, but will open up to a greater or less extent and heal by second intention. The bronchial stump, therefore, should be covered over with mediastinal pleura, as well as neighboring areolar tissue. At first, great difficulty was experienced in obtaining enough mediastinal pleura, particularly on the left side, to cover the stump. With patience, the pleura covering the aortic arch and the first portion of the descending thoracic aorta can be

dissected off and sutured over the stump. As there is apt to be a space remaining between the end of the bronchial stump and the sutured mediastinal pleura because of the bulging of the aorta into the thoracic cavity, it would seem advisable to approximate the pleura carefully to the cut end by placing two sutures, anteriorly and posteriorly, superficially in the peribronchial

FIG. 35.—Shows same type of closure on right side as Figure 34, on left side.

fibrous tissues, proximal to the cut end. This ensures prompt apposition of the cut end of the stump to the overlying mediastinal pleura, or areolar tissue. In the human being the mediastinal shift is not so immediate or so extensive as in the dog so that other means to accomplish this end, such as sutures, must be resorted to (Figs. 34 and 35). If only an upper or lower leaf of mediastinal pleura is available, it should be used. The stump may be sutured down to the tissue immediately anterior to the vertebral column or the wall of the esophagus may be employed on the left side as well as the outer covering of the pericardial sac. On the right side the mediastinal pleural membrane is usually more abundant, but in two cases in which a considerable amount had to be sacrified in the removal of the tumor, the azygos vein was ligated, divided, and sutured over the bronchial stump. Likewise, in one case a sufficient length of the pulmonary artery distal to its ligated portion was available for covering the stump of the bronchus on the left side. Mediastinal pleura is to be preferred, but when unprocurable other tissues may be substituted. The apposition of the mediastinal pleura over the cut end of the bronchial stump should be as

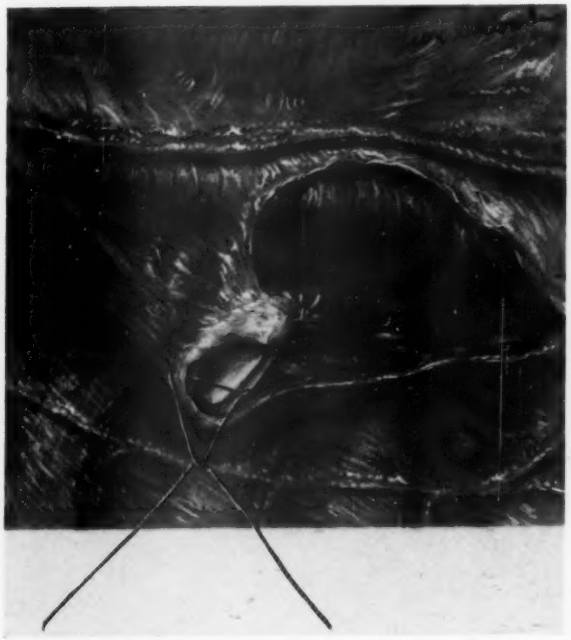

FIG. 36.—Method of pulling mediastinal pleura over open cuff of bronchus peripheral to the suture line, when there is scarcity of mediastinal pleura.

FIG. 37.—Another method of elevating a flap of mediastinal pleura to cover over bronchial stump.

snug as possible, but openings ought to be left at either end of the suture line so that if air should leak from the bronchus an avenue of escape will have been provided (Figs. 35 and 36). In a few recent cases sulfanilamide has been dusted in the area about the bronchial stump before closure of the chest (Fig. 37).

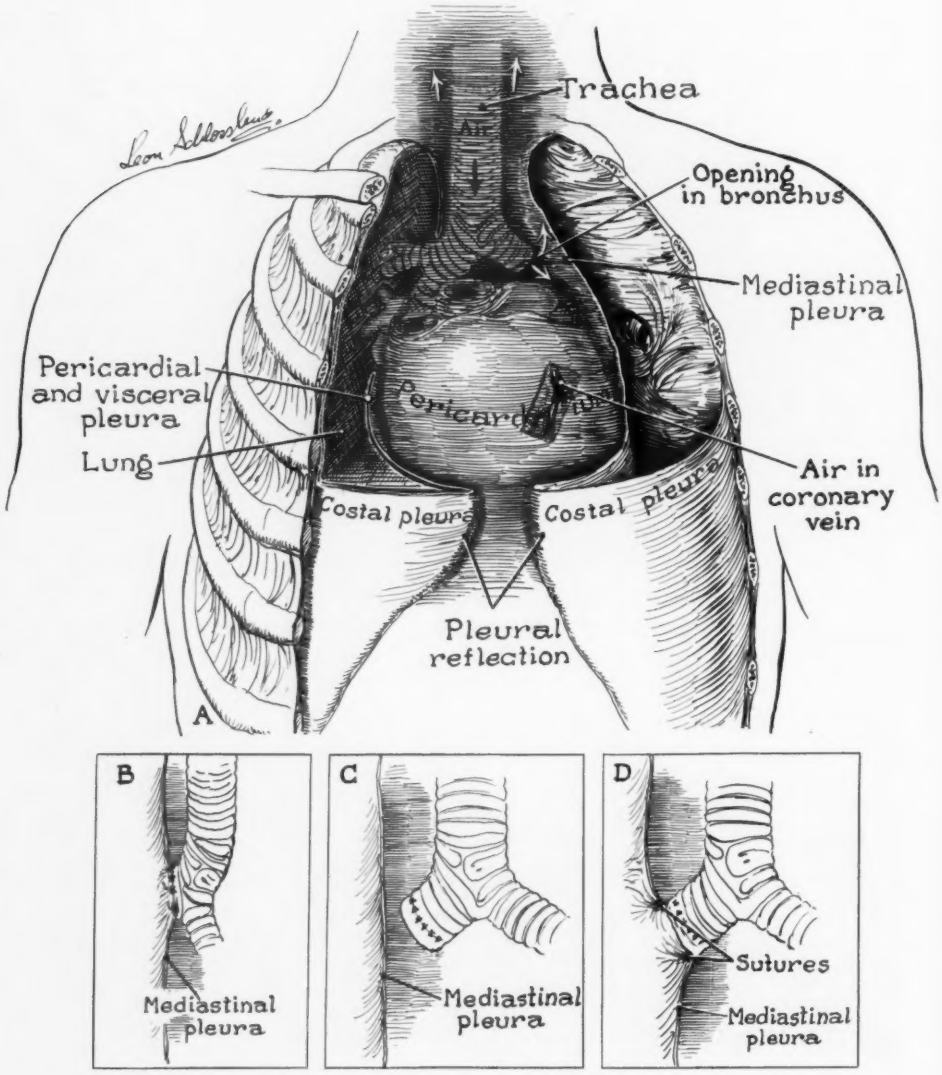

FIG. 38.—A. Shows point at which air emboli were found in coronary veins; mediastinal emphysema the result of air leaking into mediastinum unable to escape except along tissue planes, marked by white arrows. Sterile fibrous thorax already formed on operated side. B. Closure of mediastinal pleura over right bronchial stump in dog. Note close apposition of stump to mediastinal pleura, due to sutures and flexibility of mediastinum in dog. C. Space left, in patient above described, between mediastinal pleura and stump of bronchus. D. Proper apposition of bronchial stump in human, accomplished by superficial sutures in peribronchial fibrous tissue.

Two of the three deaths that have occurred in the last 27 cases of total pneumonectomy were due to leakage from the bronchus after closure by the method above described. In each, however, a technical error was made that would seem to explain the death. In one, the bronchus was clamped across before amputation with a curved Kelly clamp in order to use this as a handle to pull on the hilus. After the bronchus was cut across the clamp slipped off, and it is believed that the occluding sutures were unintentionally placed through this devitalized area. The end of the bronchus sloughed, and the patient died of a massive empyema. Since that time no clamps of any type have been used. If feasible, bronchial occlusion sutures may be placed before amputation of the lung. In the second case the mediastinal pleura was sutured tightly and completely across the hilar defect on the left side, but was not properly brought into apposition with the bronchial stump. Thus, a space was left in the mediastinum with no avenue of escape for air if the bronchus should leak. Leakage occurred on the eighth day after a previously uneventful afebrile convalescence. Mediastinal emphysema, followed by extensive subcutaneous emphysema, developed. After three days, or on the eleventh postoperative day, when the patient seemed to be improving, he suddenly died. At autopsy air emboli were observed in the anterior coronary veins (Fig. 38). The bronchus had opened, but the air could not escape. There was an enormous mediastinal emphysema. The bronchus had been closed with silk sutures as usual, and it is believed that if the mediastinal pleura had been brought into apposition with the cut end of the stump the bronchus would not have leaked. Furthermore, an opening at each end of the sutured mediastinal pleura should have been left for the escape of air. It is well to note here that mediastinal or subcutaneous emphysema or both may give rise to air emboli.

CONCLUSIONS

From this study it seems likely that the main point of healing of the bronchus is at the cut end. Every effort must be made to preserve the viability of this portion, not only by gentle handling, which avoids any form of trauma, such as crushing, cauterization, or suturing, but also by preserving the circulation in the bronchial artery. The greatest attention should be given to the placing of the occlusion sutures, particularly the number, so that interference with the circulation of the stump will be as little as possible. If the circulation is cut off, the entire end of the cuff distal to the suture line, or at least part of it may slough. Primary agglutination of this open end is thus prevented, so that when any of the occluding sutures give way a bronchial fistula develops at once. After amputation, and following the placing of the mattress sutures, it is well to allow the bronchial artery to bleed while the sutures are being tied in order to avoid occluding this vessel in one of the stitches. The bronchial stump should be brought into apposition with nearby or contiguous viable tissue, preferably mediastinal pleura. The mediastinum should not be closed tightly about the stump, but an

avenue provided for the escape of air in the event that the bronchus opens. The use of occluding nonabsorbable sutures is advocated as a means of closing the bronchial tube for a sufficient length of time to permit healing of the cut ends.

The suture line should be placed as far proximal to the cut end of the stump as possible and the minimal number of sutures employed to effect an air-tight closure. There apparently is no method or type of suture that can be relied upon of itself to secure permanent occlusion and healing of the bronchus as it had been sewed at operation. There is no autopsy evidence of this in the human being, and healing at the suture line occurred in only 18 per cent of the experimental animals, a percentage so low that the possibility of such type of healing cannot be regarded as likely in the great majority of instances. The granulation and later fibrous tissue which brings about closure of the cuff-like open end of the bronchial stump is derived mainly from the bronchial walls. In some individual instances, in both the human being and the experimental animal, the entire bronchial wall would be drawn toward the center of the lumen and sometimes actually inverted into the bronchial stump by the contracting granulation tissue, but in the majority of cases the cylindrical open end of the bronchus was filled with a mass or plug of granulation tissue that successfully occluded the stump. The bronchial epithelium grew across the closed end as a modified or somewhat flattened cell-type.

Finally, it would appear that the most important steps in the procedure to effect solid healing of the bronchus are, first, to occlude the amputated stump with as few sutures as will prevent the passage of air long enough to permit sufficient healing of the cuff of bronchus distal to the suture line; second, to avoid in every way devitalization of the terminal end of the amputated stump; and third, to effect an intimate apposition between the cut end and the surrounding areolar tissue, preferably mediastinal pleura.

REFERENCES

[1] Gluck, F.: Experimenttelles Beitrag zur Frage der Lungenextirpation. Berl. Klin. Wchnschr., **18**, 645, 1881.

[2] Block: Experimentelles zur Lungenresection. Deutsche med. Wchnschr., **7**, 634, 1881.

[3] Biondi: Lungenextirpation bei experimenteller lokalisirter tuberculose. Wien. med. Jahrb., **1**, 207, 1884.

[4] Willard, D. F.: Experiments in Pneumonectomy and Pneumotomy. Tr. Coll. Physicians, **13**, 133, 1891.

[5] Murphy, J. B.: Surgery of the Lung. J.A.M.A., **31**, 151, 1898.

[6] Tiefel, M., and Mitt, A. D.: Experimentelle studien uber Lungen and Pleura-Chirurgie. Grenzgab d. Med. u. Chir., Supplement **3**, 789, 1907.

[7] Frederick, P. L.: Über den Raumosgleich in der Brusthole nach einseitiger Lungenamputation. Arch. f. klin. Chir. Bull. **27**, 647, 1908.

[8] Danielson, W.: Beitr. zur Lungenchirurgie: Bronchotomie und Lungenresktion. Beitr. f. klin. Chir., Tubing, **60**, 94, 1908.

[9] Robinson, S.: ANNALS OF SURGERY, **47**, 184, 1908.

[10] Halsted, W. S.: Clinical and Experimental Contributions to Surgery of the Thorax. Tr. Am. Surg. Assn., **27**, 119, 1909.

[11] Meyer, W.: Pneumonectomy with Aid of Differential Air Pressure. J.A.M.A., **53**, 119, 1909.

[12] Robinson, S., and Sauerbruch, F.: Undersuchungen über die Lungenextirpation. Deutsche Ztschr. f. Chir., **102**, 542, 1909; Zentralbl. f. Chir., **37**, 391, 1910.

[13] Quinby, W. C., and Morse, G. W.: Experimental Pneumonectomy and Application to Man. Boston M. & S. J., **165**, 121, 1911.

[14] Garré: Lungenchirurgie. Garré und Quincke, 1912.

[15] Henschen, K.: Experimente zue intrathorakalen Lungenchirurgie. Beitz. z. klin. Chir., **41**, 1433, 1914.

[16] Giertz, K. H.: Über Extirpation von Lungen und Lungenlappen mit Versorgung des Bronchialstumpfes durch frei transplantierte Fascia Lata. Zentralbl. f. Chir., **41**, 1433, 1914.

[17] Kawamura, H.: Experimentelle studien über die Lungenextirpation. Deutsche Ztschr. f. Chir., **131**, 189, 1914.

[18] Heuer, G. J., and Dunn, G. R.: Experimental Pneumonectomy. Bull. Johns Hopkins Hosp., **31**, 37, 1920.

[19] Bettman, R. B.: Experimental Closure of Large Bronchi: A Study of the Factors Concerned in Failure of the Bronchi to Heal. Arch. Surg., **8**, 418, 1924.

[20] Feiermann, J.: Zur Versorgung des Bronchialstumpfes nach Lungenamputation. Arch. f. klin. Chir., **137**, 300, 1925.

[21] Bettman, R. B., James, W. A., Tannenbaum, K., and Slobe, E.: Closure of the Bronchi in Lobectomies. Surg. Gynec. & Obst., **46**, 602, 1928.

[22] Joannides, M.: Care of Stump in Pneumonectomy and Lobectomy. Arch. Surg., **17**, 91, 1928.

[23] Schleuter, S. A., and Weidlein, I. F.: Experimental Lobectomy and Pneumonectomy. Arch. Surg., **13**, 459, 1926.

[24] Nisson, R.: Simplification of Excision. Deutsche Ztschr. f. Chir., **219**, 389, 1929.

[25] Adams, W. E.: Subtotal Atelectasis and Pneumonectomy in Dogs. Proc. Soc. Exper. Biol. & Med., **28**, 957, 1931.

[26] Blalock, A.: Studies on Bronchial Occlusion by the Method of Adams and Livingston. Surg. Gynec. & Obst., **56**, 779-781, 1933.

[27] Longacre, J. J.: Experimental Pneumonectomy. Jour. Thoracic Surg., **4**, 587, 1934-35.

[28] Thomas, L. C., Behrend, A., and Mann, F. C.: Experimental Pneumonectomy. Jour. Thoracic Surg., **6**, 677, 1936-37.

[29] Taffel, M.: Repair of Tracheal and Bronchial Defects with Free Fascia Grafts. Surgery, **8**, 56, 1940.

[30] Rienhoff, W. F.: Graded Pneumonectomy in the Treatment of Tumors of the Lung. Bull. Johns Hopkins Hosp., **64**, 167-194, 1939.

[31] Stafford. E. S.: Experimental Pneumonectomy with Obliteration of the Bronchial Stump. Jour. Thoracic Surg., **10**, 480, 1941.

DISCUSSION.—DR. EVARTS A. GRAHAM (St. Louis, Mo.): I agree fully with Dr. Rienhoff that the question of securing permanent closure of the bronchus is one of the major problems confronting us with the technical features of the operation of total pneumonectomy. I agree also fully with him that the operation of total pneumonectomy is probably going to be done more and more. The chief indication for it will be bronchogenic carcinoma, which as you all know is a very common disease. It is not a very unusual condition, but it is at least of the same order of frequency as cancer of the colon, including the rectum, and probably is even of a greater order of frequency.

The difficulties that confront one in the closure of the bronchus, as he has said, are chiefly, again in my experience, on the right side. There is not nearly so much difficulty on the left side.

These experiments which have been shown have been most illuminating to me. I had not realized that in the closure of the bronchus, that apparently stayed closed when closed by mattress silk sutures, a method which I have used in recent years, these silk sutures did

cut through so frequently, as he has indicated. My difficulty in using mediastinal pleura, as he has represented so beautifully on these drawings, has been of several sorts. In the first place, it is not easy by any means to find mediastinal pleura that can be drawn over. The pleura is, of course, exceedingly thin. It is so thin that it is transparent. One cannot put any tension on it whatever without tearing it. I have succeeded several times in getting what I thought was an effective closure of the bronchus with mediastinal pleura, with a method somewhat similar to what he has described, and have seen the pleural flap tear out when the patient had a violent cough or an unusually violent inspiratory act.

Dr. Churchill some time ago asked me why I did not use free pleural transplants, as he had used them with considerable success. I confess I had not tried it until he suggested it to me, because I did not think it would work, but since his suggestion to me I have tried it on a number of cases, and I have found that I have had a fair degree of satisfaction with it.

I have also tried pedicle-flaps from the pleura of the chest wall, with the idea that they would preserve the circulation longer. I have had a fair degree of success with those, but still the problem remains.

Now I think that one of the fundamental difficulties about the healing of the bronchus is not only the anatomic features and the question of having it covered with pleura, but the question of infection. If all of the bronchi in the human being which we had to close were as sterile as those of the dog there would be less difficulty with the permanent closure, but in most cases in which a pneumonectomy is indicated there is infection present, and infection of a highly virulent type. With anaerobic putrefactive organisms the sulfonamide drugs, at least in my experience, are ineffective, and I know of no application of any antiseptic substance of any sort which is effective in a practical manner, that is to say, in any manner in which it can be applied to the prevention of infection in these cases.

Consequently, I fear that unless one can devise some more certain method than I know anything about at the present time, we are still going to have to face this very difficult problem of subsequently breaking open the bronchial stump with infection of the pleural cavity.

That brings me to one thing more, which concerns the remarks that I made when I was discussing the previous papers. One way to prevent a serious infection from an open bronchial stump is to do a thoracoplasty at the time of the total pneumonectomy, which will eliminate any pleural cavity to be infected.

The dangers of the simultaneous thoracoplasty coincident with the total pneumonectomy, I have already alluded to, but from the ideal standpoint, if we could do safely a thoracoplasty at the same time as a total pneumonectomy, I do not think the question of closure of the bronchial stump would continue to be anything of major importance.

Now, just a word or two more. This perhaps is dragging things in a little bit by the "coat tail," but I hear among groups of people who are not familiar with what has been going on in chest surgery great pessimism expressed aobut the operation of total pneumonectomy, particularly with reference to carcinoma of the bronchus. Consequently, I always like to seize upon an opportunity to do a little propaganda. There is a feeling: What difference does it make whether you do a pneumonectomy or not on a patient with bronchogenic carcinoma? You are not going to get anywhere anyway. He is going to die pretty soon of cancer. What is the use of operating upon him and subjecting him to all this trouble?

I would like to say that in my own experience now I have one patient perfectly well and living nine years afterward; another patient six years and five months afterward; another patient five years; five patients, three years; and a very considerable number less than that, who are living and apparently free from any evidence of recurrence of carcinoma. It seems to me that these figures are sufficiently good evidence of the fact that the operation is worth while, and that it is essential, therefore, that we go on and develop to as good a point as possible technical perfection, so that the mortality will be less.

Dr. Blades and I have had 76 total pneumonectomies. Of these, 59 were for bronchogenic carcinoma, and 17 for other conditions. Although the operation must still be regarded as a very serious one, we are pleased that our operative mortality is steadily declining. During the period beginning with January 1, 1939, we have had 48 cases of total pneumonectomy for bronchogenic carcinoma with 18 hospital deaths (a mortality of 37 per cent). When the operation is carried out for conditions other than carcinoma the mortality is considerably less. In 17 noncancer cases there were four hospital deaths (a mortality of 23 per cent).

DR. NORMAN S. SHENSTONE (Toronto, Canada): A year ago in Toronto, at the meeting of the American Association for Thoracic Surgery, I described a simple method of closing the bronchus after pneumonectomy. I should like to show the illustrating slide to this association, and also to report the results we have obtained.

(Slide) In the technic that we follow the dissection of all the other structures of the hilus is carried out before dealing with the bronchus. We believe that by this sequence the operation is made easier and the danger of infection reduced to a minimum. The bronchus is divided about one-eighth of an inch distal to a pair of light Kocher-style of forceps applied as close as possible to the trachea and the cut margins are approximated antero-posteriorly by three interrupted sutures of fine silk supplemented by a running suture of catgut. Following this procedure the stump is powdered with sulphathiazole, displaced into the mediastinum, and finally covered by pleura.

We have operated upon 23 consecutive cases by this method, seven for carcinoma, five for adenoma, and seven for various forms of tuberculosis, mostly bronchial stenosis. In only one of these has an open fistula developed and that in a case of very active unilateral tuberculosis, in which the bronchus opened two weeks after the primary operation. I do not believe that the method of closure can be blamed in this particular case, because it was a very doubtful case for surgery.

DR. ALTON OCHSNER (New Orleans, La.): I would like to emphasize one point, and that is one which has not been mentioned yet, namely, a cause of failure of closure of the bronchus which we have encountered. Out of the series of 32 total pneumonectomies for pneumoplastic disease we have had three cases in which there has been a failure of closure. Two of these have been in patients who have had extensive preoperative irradiation. We feel at the present time that this is a definite contraindication to surgery.

The only other patient in whom we have had difficulty, as far as closure is concerned, was a patient in whom we could not satisfactorily pleuralize the mediastinum. The simplicity with which this can be accomplished is exemplified by some experiments that Dr. De Bakey, in our clinic, has done. He has shown in animals that the simple closure of the bronchus by means of a silver clip, similar to the clip the neurosurgeons use, will satisfactorily close the bronchus and satisfactory healing will occur. We have never had quite enough nerve to try this in humans, but I am sure it would be true.

The technic that we have used has been very much the same as Dr. Shenstone's. We have used a crushing clamp, and applied mattress cotton sutures, sutures proximal to the crushing clamp. After removing the clamp and tying these sutures, we put in through-and-through sutures over the end. But we have been extremely careful, and have been influenced by Dr. Rienhoff's earlier papers in regard to this, to pleuralize the wound. If we could not accomplish it with a flap, we did it with a free graft, and have had no occasion to fear this method of closure, except in those cases in which there has been extensive irradiation.

DR. ALFRED BLALOCK (Baltimore, Md.): I think that Dr. Rienhoff, because of lack of time, did not state the number of experiments which he performed in which no sutures whatever were placed in the bronchus. I have been fortunate in seeing some of these experiments, and I must say I should not have thought previously that one would be able to produce an air-tight closure of the bronchus simply by approximating with several sutures the thin pleura which lies near the end of the divided bronchus. It is obvious that in the case of patients Dr. Rienhoff does not recommend an omission of sutures in the bronchus. Even though the sutures in the bronchus may not hold permanently, in most instances they allow time for the pleura to heal over the end of the bronchus.

The importance of this paper to me is that it is a fundamental study in wound healing in which the particular tissue happens to be the bronchus.

DR. FRANK H. LAHEY (Boston, Mass.): I particularly wanted to wait until the thoracic surgeons had completed their remarks before I arose, solely in the interests of war surgery, with the idea that the small note regarding cardiac arrest for 20 minutes with complete recovery without cerebral damage, which was recently published in the Journal of the American Medical Association, might not have been observed by some of the members of this Association. I am very sure that if this war goes on we may all possibly have to do war surgery, involved in which will be some thoracic surgery. The event which occurred in our clinic undoubtedly has previously occurred and will occur again and again,

that is, complete cardiac arrest during lobectomy. I am not aware, however, that its successful management has ever been accomplished and reported before.

I believe it is valuable for everyone to have in mind how feasible it is, by cooperation between the anesthetist and the surgeon, with the patient's chest open, to maintain circulation so that at least, as occurred in this single case, no cerebral damage will result with an arrest of the heart for a period of 20 minutes. This is not a case in which there was any doubt. Anesthesia records accurately kept and observations by competent men, with the patient's chest open, substantiate the certainty of these facts.

Here is a case in which, perhaps as a result of the vagovagal reflex, all cardiac action ceased for 20 minutes, but with the anesthetist, Dr. Hand, producing artificial breathing with the anesthesia bag, one could demonstrate, with the chest open, that the expansion of the lung filled the heart and substituted for the diastole, and with Dr. Herbert Adams, the surgeon, contracting the heart manually, produced the systole. With these manipulations, circulation was maintained, cardiac action was completely restored at the end of 20 minutes and the patient recovered with complete mental clearness. A negative electro-encephalogram was obtained, and now the patient is entirely well over a period of months.

I again wish to state that this accident will happen in thoracic surgery, that it will happen in war surgery, and it is extremely important for us all to remember that it is possible by cooperation between an anesthetist and a surgeon, either with the patient's chest open or through the diaphragm, to manually maintain circulation while efforts are being made to restore cardiac action.

DR. WILLIAM F. RIENHOFF, JR. (closing): I would like to thank Dr. Blalock for his discussion, and I will first answer his question, because in my haste, as he suggested, I neglected to mention the data which he has called attention to. The second series consisted of 48 dogs and, as in the first series, there were no operative deaths or instances of leakage of the bronchus, notwithstanding the fact that no sutures were used to occlude the blind end of the bronchus. There were in this series two deaths from distemper. In the dog there is always an abundance of mediastinal pleura which is ready at hand and not the slightest difficulty was ever experienced in obtaining a sufficient amount to cover the end of the bronchus. As Dr. Blalock suggested, we do not advocate using only the mediastinal pleura in human beings, but wish to emphasize that this is a very important step in the closure of the bronchus following total pneumonectomy in the human being, and it should be pointed out that it is our opinion that interrupted mattress sutures of nonabsorbable material, preferably of silk or cotton, should be used to occlude the airway or primary bronchus in the human, and considered only a temporary measure until the vital end of the blind end of the stump has had sufficient time to become occluded by the healing, of its own and contiguous tissue, in the mediastinum. One should abstain from all forms of trauma, such as cauterization, any type of crushing or even the placing of sutures in the end of the cuff.

In answer to Dr. Graham, it is of course possible that in some cases, particularly on the left side, adequate mediastinal pleura may not be available for satisfactory covering of the bronchial stump. In our recent cases, the last 30 to be exact, of total pneumonectomy in the human, due to a more deliberate and painstaking mobilization of the pleura, we have not experienced any difficulty in being able to close over the raw area of the hilus of the lung with this membrane. Particularly is this true if the hilar structures are uninvaded. If the structures are invaded it is very questionable whether one should attempt to do a total pneumonectomy. It is possible to dissect the mediastinal pleura on the left side off the anterior surface of the aorta, mobilize it from the anterior surface of the aorta as well and obtain enough to subtend this space inside the curvature of the aorta, thus bringing this posterior leaf of mediastinal pleura sufficiently forward to suture it to the anterior leaf. It is necessary also, in this event, to suture the pleura to the peribronchial fibrous tissue so that the end of the cuff and nonserous surface of the pleura are brought into intimate contact. In regard to Dr. Graham's suggestion about thoracoplasties, we have not found it necessary to perform thoracoplasties at the same time or previous to the total pneumonectomy. However, in three cases, when postoperative bronchial fistulæ developed resulting in a rather large infected dead space occupying part of the former pleural cavity, it was necessary to perform a posterior thoracoplasty in three stages. This procedure was completely successful in obliterating the dead space and bringing about closure of the bronchus, undoubtedly because of the approximation of the lateral chest wall to the mediastinal surface. Unquestionably, in Dr. Graham's experience thoracoplasties have relieved some

respiratory difficulties in patients which he has discussed in the past, and I am certain that his experience in this respect is far greater than mine. Undoubtedly this procedure is a most valuable one as an adjunct in certain cases of total pneumonectomy.

Ultimately the conclusion will probably be that the majority of human beings who have a total pneumonectomy will not need a thoracoplasty, but there are unquestionably quite a number that either because of respiratory difficulties, postoperative discomfort or postoperative infection will be benefited by such a procedure.

It is very interesting that Dr. Shenstone's experience with closure of the bronchus has been quite successful, indeed, although the technic that he has employed has varied considerably from the one that we have discussed. I cannot help reiterating that I think the main point of healing of the bronchus after amputation regardless of the type of sutures used is in, and at the cut end, certainly in the great majority of instances. Dr. Shenstone's results, although his series of cases is very small, would suggest that as in many other surgical procedures dealing with other organs in the body that there are several ways of accomplishing a thing successfully.

THE EFFECT OF PNEUMONECTOMY UPON CARDIOPULMONARY FUNCTION IN ADULT PATIENTS* †

ANDRÉ COURNAND, M.D., AND FRANK B. BERRY, M.D.
NEW YORK, N. Y.

FROM THE DEPARTMENTS OF MEDICINE AND OF SURGERY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, NEW YORK CITY, AND THE TUBERCULOSIS SERVICE (FIRST DIVISION, COLUMBIA UNIVERSITY), BELLEVUE HOSPITAL, NEW YORK CITY.

IN RECENT YEARS pneumonectomy has become an accepted method of treatment of malignant and benign tumors of the bronchus, and of various types of chronic pulmonary suppuration. Clinical experience has repeatedly demonstrated that the surgical ablation of one of a pair of as vitally important organs as the lungs is compatible with survival and maintenance of a fairly high degree of physical activity. Studies on the physiologic effect of pneumonectomy, until recently,[1, 2] have been almost exclusively experimental. The observations of Bremer[3] on cats, and of Longacre, Carter, *et al.*,[4, 5] on dogs are best known. It was shown by Longacre, Carter, *et al.*, in a series of experiments covering several years, that age at the time of the lung resection influences (1) the subsequent behavior of the dogs under conditions of physical stress; and (2) the later development of hyperplasia and/or emphysema in the remaining lung. However important these experiments may be, to extend their conclusions to human subjects would fail to recognize fundamental differences encountered in experimental and clinical conditions. For example, the highly mobile mediastinum of the dog has not its counterpart in man, and, in the latter, the remaining lung is quite frequently already the site of pathologic changes. Aside from information of theoretic interest regarding the immediate and remote effects of pneumonectomy upon pulmonary function, physiologic studies in man may be of practical value in individual cases, chiefly in helping to decide which are the most favorable conditions for the maintenance of a high degree of functional efficiency in the remaining lung. They may be especially contributory to the problems of optimum position of the mediastinum and of supplemental thoracoplasty. During the past several years, on the Tuberculosis Service at Bellevue Hospital, under a grant of the Commonwealth Fund, a method for the study of pulmonary function and of cardiocirculatory function, insofar as it is related to the former, has been developed,[6] and the tests devised were used in various chronic pulmonary diseases and in surgical chest conditions.[7, 8] Already, reports have been made upon the late effect of pneumonectomy in children,[1] and the immediate postoperative influence of pneumonectomy upon the state of respiratory gases in the arterial blood of adult subjects.[2] The present report, based upon a

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† Under a grant from the Commonwealth Fund.

study of 12 subjects, is concerned with various physiologic problems arising as a result of pneumonectomy performed in adults.

Material for Study—Physical characteristics and clinical data concerning the 12 subjects studied have been tabulated in Table I. There were one

TABLE I

PHYSICAL CHARACTERISTICS AND CLINICAL DATA ON THE 12 PATIENTS STUDIED

							Time of Study†				
Pt.	Sex	Age Yrs.	Ht. Cm.	Wt.* Kg.	Body Surface* Sq. M.	Diagnosis	$\bar{a}$ pn.	p pn.	$\bar{p}$ Suppl. Thoraco.	Media-stinal Mobility‡	Follow-Up after Pneumonectomy
W. J.	M.	53	160	54 47	1.48 1.56	Ca. rt. M. L. bronchus	+	+	+	+	Survival 2 years, active
W. W.	M.	64	175	64 67	1.78 1.81	Ca. lt. U. L. bronchus	+	+	0	0	Survival 18 mos., active
D. M.	M.	62	178	57 65	1.72 1.80	Ca. lt. U. L. bronchus	+	+	0	++	Survival 15 mos., active
T. G.	M.	43	169	62 57	1.71 1.64	Ca. rt. main bronchus	+	+	0		Death—metastasis, 7 mos.
E. B.	M.	31	190	98 103	2.18 2.32	Ca. lt. main bronchus	+	+	0	+	Death—metastasis, 20 mos.
R. B.	M.	60	175	55 62.5	1.65 1.76	Ca. lt. L. L. bronchus	+	+	0	0	Survival 1 year. Metastasis chest wall.
W. H.	M.	47	168	72.5	1.82	Ca. lt. main bronchus	0	+	0	0	Death—metastasis, 21 months
E. R.	M.	32	174	54.5 53	1.66 1.64	Bronchiectasis left upper and lower lobe	+	+	+	0	Survival 9 mos. Recent thoraco-plasty
A. M.	F.	23	148	44.5 37.5	1.35 1.25	Bronchiectasis	+	0	+	0	Survival 12 mos., active
F. I.	M.	46	178.5	70 65	1.88 1.82	Endobronchial Tbc. Obstruction rt. main bronchus	+	0	+	0	Survival 9 mos., active
M. K.	M.	37	169	66	1.76	Chronic lung abscess, rt.	0	+	0	0	Survival 31 mos., active
K. G.	M.	33	175	83	1.99	Traumatic fracture rt. main bronchus with complete obstruction	0	+	0	0	Survival 2 yrs., active

*The two figures correspond to pre- and postoperative weight and body-surface area.
†Time of study—$\bar{a}$ pn. = before pneumonectomy.
$\bar{p}$ pn. = after pneumonectomy.
$\bar{p}$ Suppl. Thoraco. = after supplemental thoracoplasty.
‡Mediastinal mobility after pneumonectomy.

female and 11 males, with ages from 23 to 64 years. Pneumonectomy was undertaken in seven instances after a diagnosis of carcinoma of the bronchus had been established; in three, for chronic suppuration of the lung; in one, after traumatic fracture of a main bronchus and resulting stenosis; and in one case, for almost complete obstruction of a main bronchus secondary to an endobronchial tuberculosis.

In six subjects the studies were carried out before pneumonectomy and at various intervals afterwards, when the patients had resumed normal activity; in two of these, studies were again repeated after a supplemental thoracoplasty had been completed. In two patients, studies were made before ablation of the lung and again after the pneumonectomy had been supplemented by a thoracoplasty, without measurements in the interval. In the four remaining cases measurements were made singly or repeatedly after pneumonectomy.

Method of Study—In Table II, information concerning the functions studied, and the measurements made, along with references regarding technics, normal control values, etc., have been summarized.

Briefly stated, the measurements were as follows: (A) Lung volumes and subdivisions; (B) maximum breathing capacity; (C) ventilation, breathing reserve, and respiratory gas exchange under basal conditions, during moderate exercise, and during a five-minute period of recovery following exercise;

TABLE II

SUMMARY OF MEASUREMENTS OF CARDIOPULMONARY FUNCTION

A. VENTILATORY FUNCTION

Measurement	Definition	Significance	References
Lung Volume in liters		Description of available air space for ventilation	Technics — formula for prediction of normal values according to body size, age, sex[9, 10, 11]
Vital Capacity (V. C.)	Volume of maximally deep breath		
Residual Air (R. A.)	Volume in lung after extreme expiration		
Total Capacity (T. C.) (T. C. = V. C. + R. A.)	Total volume in deepest inspiration		
Ratio $\frac{\text{R. A.}}{\text{T. C.}} \times 100$	Residual air expressed as per cent of total capacity	Expression of degree of pulmonary distention, physiologic or pathologic (emphysema)	
Maximum Breathing Capacity—lit./min. (M. B. C.)	Maximum volume of air that can be displaced per minute	Estimation of the efficiency of the chest bellows in displacing air per unit of time	Technics[6, 12]—formula for prediction M. B. C. lit./min. = 80.9 × B. S. in sq. m. = 29.3
Ventilation in liters per min. per sq. m. body surface (V):	Actual volume of air per minute displaced in a given physical state		Technic[6]. Normal control values—according to age, sex (unpublished data)
(1) Basal			
(2) Moderate exercise			
(3) During 5 minutes of recovery from moderate exercise			
Breathing Reserve (B. R. = M. B. C. − V)	Excess breathing capacity beyond actual ventilation in a given state		
Ratio $\frac{\text{B. R.}}{\text{M. B. C.}} \times 100$	Breathing reserve expressed as per cent of maximum breathing capacity	Provides a numerical estimation of dyspnea in pulmonary insufficiency	Relation with dyspnea.[6] Normal control values according to age, sex (unpublished data)

B. ALVEOLORESPIRATORY FUNCTION

Measurement	Definition	Significance	References
Pulmonary Emptying Rate	Nitrogen concentration of alveolar air after 7 minutes' pure oxygen breathing	A numerical estimate of adequacy of inspired air distribution in alveoli	Technic and range of variation[11]
Respiratory Gas Exchange:	Carbon dioxide output and oxygen intake in a given physical state expressed		Technic.[6] Normal range according to age and sex (unpublished data)
(1) Basal			
(2) Moderate exercise			
(3) During 5 minutes of recovery	(a) in cc./sq. m./min.	(a) Measures amount of gas exchange used in a given physical state	
	(b) in cc./liter vent.	(b) Gives efficiency of ventilation in providing O_2 absorption (utilization)	
State of Respiratory Gases in Arterial Blood:	(a) Oxyhemoglobin saturation—%	Measures effectiveness of lungs in aerating blood and state of respiratory gases reaching tissues	Technic — Normal range[6]
(1) Basal	(b) Carbon dioxide pressure—mm. Hg.		
(2) During early recovery from moderate exercise			

C. CARDIOPULMONARY FUNCTION

Measurement	Definition	Significance	References
Includes:			
(a) *Routine:* Arterial blood pressure Electrocardiogram Ballistocardiogram			
(b) *Cardiovascular response* to rapid intravenous saline infusion	(a) Variation of venous pressure (b) Circulation time (c) Vital capacity following infusion of 1500 cc. isotonic solution in 30 min.	Brings out latent congestive state due to back pressure from failure of left heart, of pulmonary vascular bed, or of right heart	Technic[6, 13, 14]

(D) state of respiratory gases in the arterial blood at rest and immediately after completion of the moderate exercise; and (E) variations in venous pressure, circulation time, and vital capacity following an increase in blood volume produced by a rapid intravenous infusion of 1500 cc. of a saline solution. Data available from the literature[19] and a separate study of 60 normal subjects, age 20 to 69, supplied the desired control values.

Results—Four separate headings may better describe the data obtained in this study:

(1) State of pulmonary and cardiocirculatory function after pneumonectomy in comparison with normal subjects.

(2) State of ventilatory function before and after pneumonectomy in same subjects.

(3) Influence of thoracoplasty supplementing a pneumonectomy upon the state of ventilatory function.

(4) Influence of mediastinal adjustment and preexisting pulmonary emphysema upon pulmonary function.

(1) State of Pulmonary and Cardiocirculatory Function after Pneumonectomy: Comparison with Normal Subjects—Data on ten patients are available, two subjects studied only after supplemental thoracoplasty was completed have been excluded. The ten patients have been separated into two groups according to age: Group I consists of six patients, ages ranging from 32 to 47. Group II consists of four patients, ages ranging from 53 to 66.

The predicted normal figures and the control normal figures were calculated according to data available in subjects in the same age-groups. Mean values, observed, predicted, or calculated for controls, are tabulated in Tables III to IX.

A—VENTILATORY FUNCTION

1. Lung volumes and subdivisions (Table III, Chart 1).

In both groups I and II, the mean size of the remaining lung in deepest inspiration is somewhat larger than the predicted size of one of a pair of normal lungs. This increase is due to the persistence of a large residual air volume; the remaining lung after pneumonectomy is slightly smaller at the end of a complete expiration than two normal lungs in Group I, and as large as two normal lungs in Group II. There is then evidence of lung distention after

pneumonectomy, especially in the older age-group, although the mean residual air of 37 per cent of the total capacity does indicate that if pulmonary emphysema is present, it is of mild degree, or present only in a small proportion of the group. Studies of individual data prove the latter to be the case.

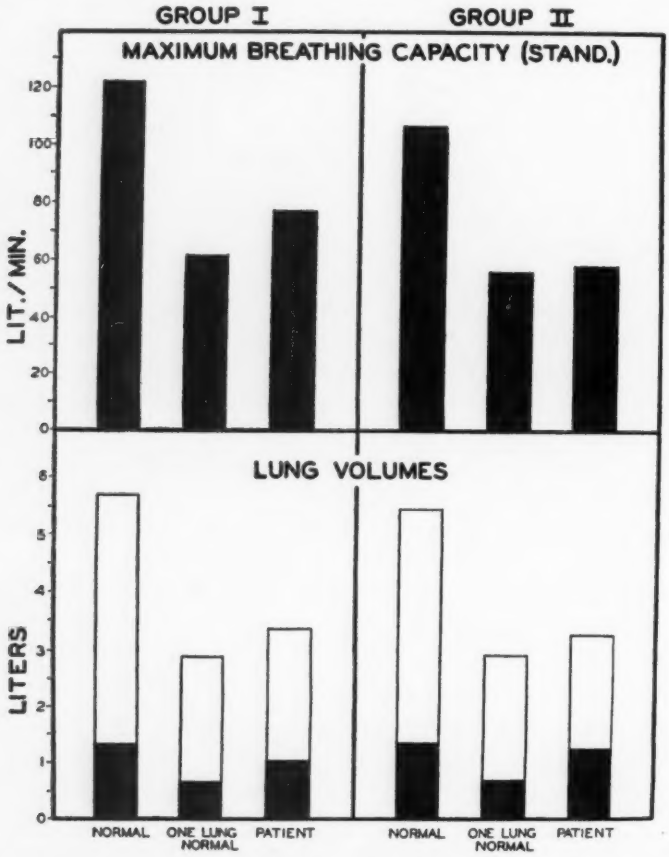


CHART 1.—Lung volumes and subdivisions in liters, and maximum breathing capacity in liters per minute. In each of the two groups, the blocks to the left = average predicted values for normal subjects of same size, sex, and age distribution; the blocks in the center = the average assumed value for one lung of the normal subjects; the blocks to the right = average observed values in patients studied after pneumonectomy. Under lung volumes, solid blocks = residual air volume; white blocks = vital capacity (complemental air + reserve air).

2. Maximum breathing capacity in liters per minute (Table III, Chart 1).

The maximal efficiency of the chest bellows in displacing air after pneumonectomy is reduced in both groups: In Group I the maximum breathing capacity is 63 per cent of the predicted value for two normal lungs, and in Group II 50 per cent. In the younger age-group, coincident with less distention, the remaining lung is more effective in circulating air than the remaining lung in the older age-group, and in addition is more effective than one of a pair of normal lungs, (maximum breathing capacity 26 per cent greater than predicted value for one lung).

TABLE III

LUNG VOLUMES* AND MAXIMUM BREATHING CAPACITY AFTER PNEUMONECTOMY

Group	Total Capacity (liters) Mean	Vital Capacity (liters) Mean	Residual Air (liters) Mean	R. A. / T. C. × 100 Mean	Maximum Breathing Capacity—Standing (liters/minute) Mean
Group I†					
Predicted					
Both lungs	5.68	4.44	1.28	22.5	121.4
One lung	2.84	2.22	0.64		60.8
Observed	3.35	2.32	1.03	30.8	76.6
Group II†:					
Predicted					
Both lungs	5.45	4.12	1.33	24.4	106.0
One lung	2.86	2.16	0.70		55.8
Observed	3.25	2.03	1.33	37.5	57.8

*Saturated dry gas at 37° C. and prevailing barometric pressure.

†Group I consists of 6 patients, age 32 to 47, and Group II of 4 patients, age 53 to 65.

Average predicted and observed values in two groups of adults after pneumonectomy.

3. Ventilation at rest, during moderate exercise, during each of five minutes of recovery (Table IV, Chart 2).

There are significant differences between the two groups: In the younger age-group the average figures of ventilation under varying states of activity are almost identical with the average control normal figures; in the older age-group, ventilation is somewhat larger than normal at rest, much more so during exercise and during recovery.

TABLE IV

VENTILATION AT REST*, DURING MODERATE EXERCISE, AND DURING EACH OF FIVE MINUTES OF RECOVERY FROM MODERATE EXERCISE, AFTER PNEUMONECTOMY

	Ventilation, liters/min./sq. m. B. S.*						
Group	Basal Mean	Exercise Mean	Rec. 1 Mean	Rec. 2 Mean	Rec. 3 Mean	Rec. 4 Mean	Rec. 5 Mean
Group I†:							
Normal controls	3.42	9.72	12.80	8.30	7.50	6.13	5.40
Patients after pneumonectomy	3.28	9.88	12.84	8.32	7.52	5.60	5.26
Group II†:							
Normal controls	3.92	11.13	14.83	10.83	8.37	7.08	6.20
Patients after pneumonectomy	4.17	15.11	15.35	13.02	10.25	8.65	7.62

*Saturated gas at 37° C. and prevailing barometric pressure.

†See Table III.

Average observed values in two groups of adults after pneumonectomy, and average values in two corresponding groups of normal subjects.

TABLE V

RATIO $\frac{\text{BREATHING RESERVE}}{\text{MAXIMUM BREATHING CAPACITY}} \times 100$ AT REST, DURING MODERATE EXERCISE, AND DURING EACH OF FIVE MINUTES OF RECOVERY, AFTER PNEUMONECTOMY

	Ratio $\frac{\text{Breathing Reserve}}{\text{Maximum Breathing Capacity}} \times 100$						
Group	Basal Mean	Exercise Mean	Rec. 1 Mean	Rec. 2 Mean	Rec. 3 Mean	Rec. 4 Mean	Rec. 5 Mean
Group I*:							
Normal controls	94.0	83.7	76.0	83.4	86.9	88.9	90.2
Patients after pneumonectomy	89.3	76.0	59.4	75.4	80.2	83.5	84.1
Group II*:							
Normal controls	91.2	79.6	67.4	76.4	81.4	84.4	86.2
Patients after pneumonectomy	86.5	51.7	49.3	57.4	66.8	71.2	74.9

*See Table III.

Average observed values in two groups of adults after pneumonectomy, and average values in two corresponding groups of normal subjects.

4. Ratio $\frac{\text{B. R.}}{\text{M. B. C.}}$ x 100, at rest, during exercise, during each of five minutes of recovery (Table V, Chart 2).

This ratio being dependent upon the values of maximum breathing capacity and of ventilation, it is not surprising to find it lower in the older age-group

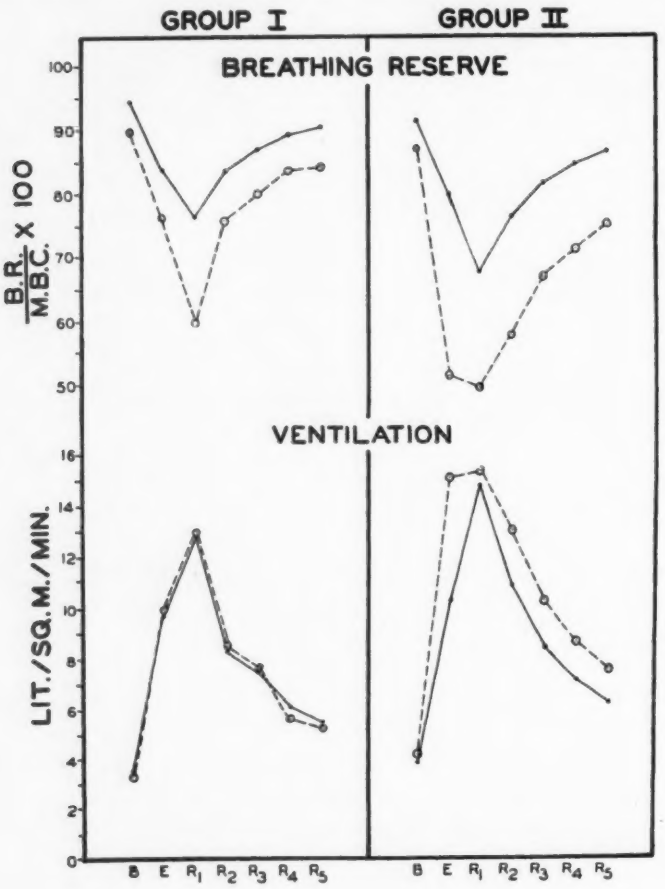


CHART 2.—Ventilation and ratio $\frac{\text{breathing reserve}}{\text{maximum breathing capacity}} \times 100$

under standard basal conditions (B), during moderate exercise (E), and each of the five minutes of recovery following moderate exercise (R_1 = 1st minute of recovery, R_2 = second minute, etc.) Solid lines = average values for normal subjects, age 30 to 50 (Group I), and 51 to 69 (Group II). Broken lines = average values in 10 patients after pneumonectomy in same age-groups.

than in the younger, especially during exercise and during the recovery period from exercise. As dyspnea usually occurs when the value of this ratio is below 60 to 70 per cent, it should be more marked and more persistent for the same degree of activity in Group II than in Group I. This is supported by observations concerning dyspnea made in both groups during the recovery period—in Group I the average duration of dyspnea following completion of the standard exercise was 33 seconds; in Group II it was 142 seconds.

Summarizing the main findings concerning the anatomic status of the remaining lung, and its ventilatory function, in ten patients after pneumonectomy: (a) The lung was somewhat distended, more so in the older group; (b) maximal efficiency of the chest bellows in displacing air with only one lung was better than predicted in the younger subjects, but just exactly as predicted in the older age-group; and (c) relative hyperventilation was present during exercise and persisted during the recovery period in the older subjects, and it further encroached upon the breathing reserve and resulted in a greater tendency to dyspnea.

B—ALVEOLORESPIRATORY FUNCTION

1. Pulmonary emptying rate: Following pneumonectomy, the average figures of nitrogen concentration in alveolar samples taken after seven minutes of pure oxygen breathing in Groups I and II, as well as individual figures, were well within normal range. Tidal air, in spite of a definite increase in residual air volume, was thus efficiently distributed during quiet breathing to the functioning alveoli of the remaining lung.

2. Respiratory gas exchange—carbon dioxide output and oxygen intake (Table VI and VII).

TABLE VI

RESPIRATORY GAS EXCHANGE. CARBON DIOXIDE OUTPUT AT REST*, DURING MODERATE EXERCISE, AND DURING FIVE MINUTES OF RECOVERY FROM MODERATE EXERCISE, AFTER PNEUMONECTOMY

Group	CO_2 Output, cc./min./sq. m. B. S.†			CO_2 Output, cc./liter vent.		
	Basal	Exercise	Recovery	Basal	Exercise	Recovery
Group I‡:						
Normal controls	104	329	1516	35.4	36.8	42.5
Patients after pneumonectomy	107	336	1449	36.7	37.6	40.4
Group II‡:						
Normal controls	104	329	1523	30.5	34.0	37.5
Patients after pneumonectomy	101	374	1601	27.9	28.5	33.2

*Under basal conditions.
†Dry gas at 0° C. and 760 mm. Hg. barometric pressure.
‡See Table III.
Average observed values in two groups of adults after pneumonectomy, and average values in two corresponding groups of normal subjects.

TABLE VII

RESPIRATORY GAS EXCHANGE. OXYGEN INTAKE AT REST*, DURING MODERATE EXERCISE, AND DURING FIVE MINUTES OF RECOVERY FROM MODERATE EXERCISE, AFTER PNEUMONECTOMY

Group	O_2 Intake, cc./min./sq. m. B. S.†			O_2 Intake, cc./liter vent.		
	Basal Mean	Exercise Mean	Recovery Mean	Basal Mean	Exercise Mean	Recovery Mean
Group I‡:						
Normal controls	134	489	1523	45.8	57.3	43.4
Patients after pneumonectomy	143	520	1524	49.1	57.5	42.9
Group II‡:						
Normal controls	130	491	1509	38.1	52.5	36.9
Patients after pneumonectomy	126	475	1438	34.9	36.7	31.0

*Under basal conditions.
†Dry gas at 0° C. and 760 mm. Hg. barometric pressure.
‡See Table III.
Average observed values in two groups of adults after pneumonectomy, and average values in two corresponding groups of normal subjects.

There are significant differences between the two groups. The average figures in Group I are but little different from the normal control values—

the direction in changes being, if anything, toward greater rather than lesser efficiency during periods of physical activity. In Group II, however, the carbon dioxide output, per minute, was larger than in the control group during exercise and recovery, and the oxygen intake per minute less during corresponding periods; hence there is evidence that efficiency in gas exchange is impaired. Particularly significant are the low rate of oxygen removal per liter of ventilation at rest and during recovery from exercise, and its total lack of increase during exercise. Two causes may be invoked to explain these changes: (a) Inefficient alveolar ventilation due to hyperventilation; and (b) inadequate increase in circulation during exertion and the following recovery period.

3. State of respiratory gases in arterial blood (Table VIII): In both groups the proportion of hemoglobin in the oxyhemoglobin state, and the tension of carbon dioxide in the blood leaving the lung, were well within normal range both at rest and after moderate exercise. This indicates that during moderate exertion the correlation between alveolar ventilation and pulmonary circulation and/or the diffusion across alveolocapillary membranes remained normal.

TABLE VIII

ARTERIAL BLOOD: STATE OF RESPIRATORY GASES AT REST AND DURING EARLY RECOVERY FROM MODERATE EXERCISE, AFTER PNEUMONECTOMY

	Oxyhemoglobin Saturation, %				CO_2 Tension in Mm. Hg.			
	Rest		Recovery		Rest		Recovery	
Group	Mean	Range	Mean	Range	Mean	Range	Mean	Range
Normal	96.2	±1.2	95.8	±1.3	43.7	±3.5	43.0	±2.4
Group I*:								
Patients after pneumonectomy	95.5		94.8		39.8		37.4	
Group II*:								
Patients after pneumonectomy	95.9		94.6		39.8		40.9	

*See Table III.

Average oxyhemoglobin saturation % and CO_2 pressure in Mm. Hg. in two groups of adults after pneumonectomy, and normal range.

Summarizing the data on gas exchange after pneumonectomy, the only abnormality noted among the ten patients after they had resumed some activity was, in the older patients, lowered efficiency in supplying oxygen to the tissues, especially during exertion and the early recovery period. The repayment of the oxygen debt, contracted during exercise, takes longer than in the younger patients in spite of the tendency to hyperventilation noted during the short period of observation. Whether this is due to poorer alveolar ventilation occurring under stress in a lung somewhat distended, or inadequate increase in cardiac output cannot be decided on the basis of data obtained; the aeration of the blood leaving the lung remained, however, well within normal range.

C—CARDIOCIRCULATORY FUNCTION

Routine measurements of cardiocirculatory function including arterial blood pressure, electrocardiogram, and ballistocardiogram, failed to reveal any abnormality that might be connected directly to the surgical removal of the lung. One of the older subjects with auricular fibrillation, present prior to the pneumonectomy, rallied remarkably after operation; and there was no

evidence that "minimal myocardial damage," as revealed by the electrocardiogram in a few patients, was increased to any significant degree. Insofar as the infusion test was concerned (Table IX), it failed to bring out any latent congestive state due to back pressure from failure of the left heart, pulmonary vascular bed or right heart. In addition, the initial venous pressure level and the circulation time were well within normal figures; the slightly lower figures for venous pressure in Group II are of no significance, being probably due to inaccurate prediction of the exact position of the right auricle in subjects with chest inflation greater than normal.

TABLE IX

STATE OF CIRCULATION: VENOUS PRESSURE, CIRCULATION TIME, AND VITAL CAPACITY BEFORE AND AT END OF INFUSION TEST (1500 CC. SALINE IN 30 MINUTES) AFTER PNEUMONECTOMY

	Venous Pressure Mm. H_2O		Circulation Time sec.		Vital Capacity % Decrease
	Before Infusion	At End of Infusion	Before Infusion	At End of Infusion	At End of Infusion
Group	Mean	Mean	Mean	Mean	Mean
Normal range	Below 90	Increase less than 60 Mm. H_2O or final level less than 125 Mm.	Below 18 sec.	Below 20 sec.	Less than 8%
Group I:					
Patients after pneumonectomy	64	78	15.7	17.1	5.0
Group II:					
Patients after pneumonectomy	32	46	14.3	15.9	4.6

Average observed values in two groups of subjects after pneumonectomy and normal range.

In the results so far presented, the most significant findings in patients after pneumonectomy, besides an obvious decrease in size of the lungs, were: (a) A greater tendency to dyspnea in a group of subjects age 53 to 65, due to a greater decrease in the chest bellows' capacity for circulating air and a greater demand upon ventilating requirements during and following moderate exercise; and (b) a lesser efficiency in the same group to supply oxygen to the tissues during and following exercise. There was some evidence that lung distention is more a liability than an asset, both from the point of view of mechanics of the chest bellows and of gas interchange between alveoli and circulating blood.

(2) State of Ventilatory Function Before and After Pneumonectomy in the Same Subjects—To decide whether some of the findings described in the previous section may be, to some degree, unrelated to the surgical ablation of the lung itself and the intrathoracic adjustments which followed, it is important to compare data obtained before and after pneumonectomy. Such observations were made in six patients, two of them with pathology throughout an entire lung before pneumonectomy (E. B. and E. R.), and the remaining four with pathology limited to one lobe or less (W. J., V. W., D. M., and T. G.). Changes in vital capacity and residual air in the first two patients were insignificant (within 180 cc.). The maximum breathing capacity in E. B. increased by 14 liters per minute after pneumonectomy. For the other four subjects absolute decrease in vital capacity and in residual air volumes was large, as one expected, averaging 1.2 liters for vital capacity and 0.7 liters for the residual air. But, significantly enough, the percentage of the residual air in

the total capacity remained practically unchanged—38 per cent before and 40 per cent after. As three out of four of these patients belonged to Group II of the preceding section it seems, therefore, that the somewhat larger degree of lung distention noted in older subjects after pneumonectomy antedates the surgical procedure. Another interesting observation is that as the average vital capacity in these four patients decreased by 34 per cent after pneumonectomy, the average maximum breathing capacity decreased by only 21 per cent.

(3) Influence of Thoracoplasty Supplementing a Pneumonectomy upon the State of Ventilatory Function—In four patients pneumonectomy was supplemented by a thoracoplasty. In two (W. G. and E. R.), measurements were made before and after pneumonectomy and again after thoracoplasty; in the other two (F. I. and A. M.), the lung removed being functionless, measurements made before pneumonectomy were repeated only after thoracoplasty and resumption of activity.

Data summarizing many observations on W. J. (Tables X, XI and Plate I), cover prepneumonectomy, postpneumonectomy, and postthoracoplasty periods. Following pneumonectomy the maximum breathing capacity was reduced to about 50 per cent of the preoperative value, a rather considerable decrease, and, in addition, alveolar ventilation was apparently less efficient in

TABLE X

INFLUENCE OF THORACOPLASTY UPON LUNG VOLUMES AND MAXIMUM BREATHING CAPACITY IN FOUR PATIENTS AFTER COMPLETION OF PNEUMONECTOMY

Patients	State	Total Capacity (liters)	Vital Capacity (liters)	Residual Air (liters)	R. A. / T. C. × 100	Maximum Breathing Capacity—Standing (liters/minute)
W. J., male, age 53	Before pneumonectomy	6.22	4.07	2.15	34.5	90.9
	After pneumonectomy	3.63	2.14	1.49	41.1	45.8
	After thoracoplasty 1 month	2.86	1.92	0.94	33.0	65.6
	6 months	3.23	2.00	1.23	38.2	58.2
F. I., male, age 46	Before pneumonectomy	4.13	2.98	1.15	27.9	59.8
	After thoracoplasty	2.88	1.92	0.96	33.4	77.7
A. M., female, age 23	Before pneumonectomy	2.59	1.74	0.85	32.8	34.8
	After thoracoplasty	1.96	1.24	0.72	36.7	37.0
E. R., male, age 32	Before pneumonectomy	3.51	2.66	0.85	24.2	72.9
	After pneumonectomy	3.38	2.36	1.02	30.2	67.4
	After thoracoplasty	3.13	2.25	0.88	28.0	64.0

TABLE XI

INFLUENCE OF THORACOPLASTY UPON BREATHING RESERVE AND RATE OF O_2 INTAKE AT REST, DURING MODERATE EXERCISE AND DURING RECOVERY FROM MODERATE EXERCISE, IN ONE PATIENT AFTER PNEUMONECTOMY

	Ratio: Breathing Reserve / Maximum Breathing Capacity × 100							Rate of O_2 Intake cc./lit. vent.		
			Recovery							Average of 5 min.
Patient State	Rest	Exercise	1 min.	2 min.	3 min.	4 min.	5 min.	Rest	Exercise	Recovery
W. J. Before pneumonectomy	91.0	79.6	59.1	69.8	75.6	83.0	85.0	39.2	49.1	30.7
After pneumonectomy	86.4	53.7	53.9	61.6	71.0	75.6	79.5	36.4	37.1	32.8
After thoracoplasty, 6 months	89.8	69.6	59.3	69.2	71.8	79.9	81.2	41.4	43.1	36.2

supplying oxygen for tissue needs. It was thought that a plausible explanation for the unfavorable functional result was moderate relative overdistention of the remaining lung as successive measurements had shown a steady increase of the percentage of residual air in the total capacity. To control this distention thoracoplasty was decided upon. One month after its completion the percentage of residual air in the total capacity had returned to the prepneumonectomy level and the maximum breathing capacity was nearly 20 liters larger than before thoracoplasty. In subsequent months some of these gains were partly reduced as scoliosis tended to develop, but as some beneficial effects still remained, dyspnea was less marked after exercise than it was during the prethoracoplasty studies and the efficiency in providing oxygen absorption was considerably improved.

In patients F. I. and A. M. the influence of thorcoplasty is more difficult to evaluate because no data are available of the state of the pulmonary function after pneumonectomy. It is, however, suggestive that thoracoplasty little impaired the ventilating function as in both cases, especially F. I., the maximum breathing capacity after thoracoplasty was larger than before pneumonectomy.

In patient E. R., lung volume measurements and maximum breathing capacity were practically unchanged after pneumonectomy and after thoracoplasty.

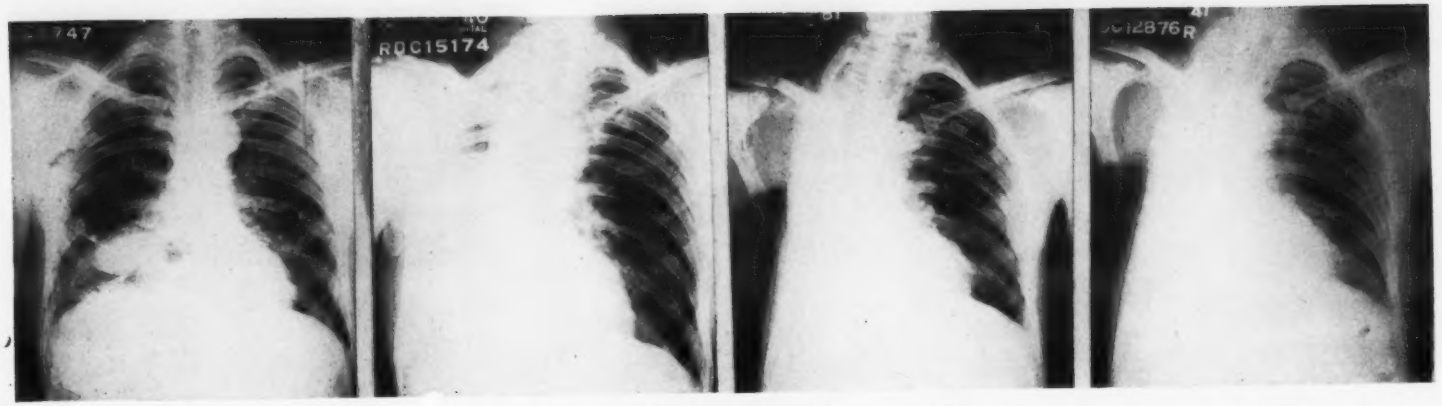
It appears, therefore, that thoracoplasty after pneumonectomy does not impair further the mechanics of the chest bellows, and if scoliosis is successfully controlled, it may well improve pulmonary function by preventing lung overdistention.

(4) Influence upon Pulmonary Function of Mediastinal Adjustments and Preexisting Pulmonary Emphysema—Among the 12 patients studied there was only one who exhibited any significant clinical evidence of pulmonary emphysema before pneumonectomy. This man also presented a very difficult problem of mediastinal adjustment, and management of the remaining lung. D. M., age 62, was first studied, November 16, 1940 (Plate II, No. 1), after a carcinoma of the left upper lobe bronchus had been diagnosed and verified by biopsy. Lung volume measurements confirmed the clinical impression of pulmonary emphysema and the high ratio of residual air ($\frac{\text{R.A.}}{\text{T.C.}} \times 100$) indicated a marked degree of emphysema. Other measurements revealed that there was a considerable limitation in maximum breathing capacity, that oxygen absorption was not efficiently managed at rest or during increased physical activity, and that the arterial oxyhemoglobin saturation was somewhat below normal.

After pneumonectomy was performed the patient had to be kept in an oxygen tent for a period of three weeks, and suffered from obvious symptoms of anoxia as soon as he breathed atmospheric air. On December 14, 1940, (Plate II, No. 2) the residual air of the remaining right lung was almost exactly equal to that of both lungs prior to pneumonectomy. It constituted 71 per cent of the total capacity, indicating an extreme degree of emphysema.

PLATE I

Patient W. J.



I	II		III	IV
6.22	3.63	Total Capacity/(liters)	2.86	3.23
4.07	2.14	Vital Capacity/(liters)	1.92	2.00
2.15	1.49	Residual Air/(liters)	0.94	1.23
34.5	41.1	$\frac{\text{R. A.}}{\text{T. C.}} \times 100$	33.0	38.2
90.9	45.8	Maximum Breathing Capacity (lit./min.)	65.6	58.2

Influence of thoracoplasty performed after pneumonectomy upon lung volumes and maximum breathing capacity:
I. Before pneumonectomy. II. After pneumonectomy. III. One month after thoracoplasty. IV. Six months after thoracoplasty.

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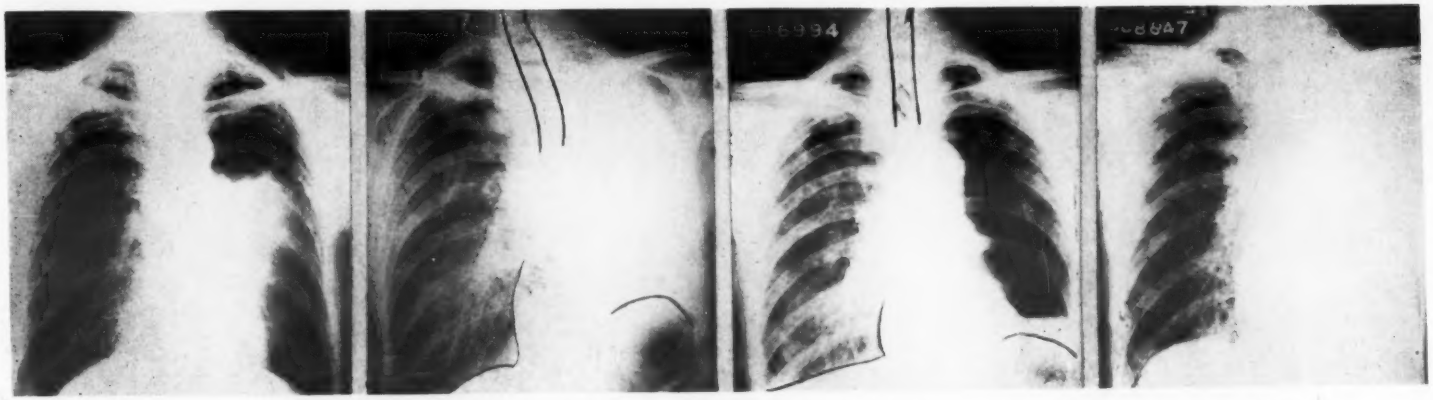
PLATE II

Patient D. M.



I 11/16/40	II 12/14/40		III 12/28/40	IV 11/13/41
5.01	3.59	Total Capacity/(liters)	2.83	3.47
2.36	1.04	Vital Capacity/(liters)	1.33	1.69
2.65	2.55	Residual Air/(liters)	1.50	1.48
53.0	71.0	$\frac{\text{R. A.}}{\text{T. C.}} \times 100$	52.8	42.6
37.8		Maximum Breathing Capacity (lit./min.)		40.7
90.7	84.1	Arterial Oxyhemoglobin Saturation at Rest (%)	91.4	95.6

Influence of the state of lung distention upon various measurements of pulmonary function:
I. Before pneumonectomy. II. After pneumonectomy, note low right diaphragm, and displacement of trachea into left chest. III. Few days later, after air replacement in left chest. IV. One year later, after oleothorax.

Defective alveolar ventilation at that time resulted in low oxygen saturation in the arterial blood. Obviously the distention of the remaining emphysematous lung, clinically characterized by a deviation of the trachea to the left and a very low right diaphragm, was not of a compensatory nature. Physiologically, it was undesirable, and, anatomically, it was probably related to low total pressure of gases in solution in the fluid filling the deserted left hemithorax and subsequent distention of the contralateral lung.

With the mediastinum back in midline following air replacement (Plate II, No. 3) the residual air decreased to 52.8 per cent, and the arterial oxyhemoglobin saturation returned to preoperative value.

In order to maintain the mediastinum in the midline, oil was introduced and substituted for air and fluid. Frequent check-ups have prevented recurring overdistention of the right lung. One year later (Plate II, No. 4) with slight evidence of shift of the mediastinum *towards the right side,* and probably because of better muscular tone the maximum breathing capacity with one lung was almost identical to values obtained with two lungs, the percentage of residual air was lower than before pneumonectomy, and the arterial oxyhemoglobin saturation was normal. Concomitantly, the performance of the moderate exercise did not cause any more dyspnea than when the patient had two lungs.

The findings in this case suggest that the presence of emphysema is not an obstacle to satisfactory functional results if proper care is taken after pneumonectomy to avoid distention of the remaining lung.

Discussion—In discussing the effect of pneumonectomy upon pulmonary and cardiocirculatory function in animals, and in man, early and late physiologic adjustments should be considered separately.

There is little data concerning the hemodynamic adjustments associated with the rapid rerouting of the entire stroke-volume of the right heart through the vascular bed of a single lung; in particular, no information regarding blood pressure changes in the lesser circulation, velocity of blood flow in the pulmonary circuit, *etc.* Yet the failure of proper adjustment in man is probably the most important cause of early postoperative death. It is announced by a syndrome resembling acute pulmonary edema oftentimes described as "drowned lung." The exact mechanism of this syndrome is unknown, its true nature even doubtful, some ascribing it to acute cardiac failure, others to acute pulmonary failure. The tests of cardiocirculatory function, described in this report, are of no avail in predicting, before operation, the chances that such a complication may develop. In one patient who died from "drowned lung," within 24 hours after pneumonectomy, the response to the infusion test performed prior to pneumonectomy had been absolutely normal.

In very rare instances a classical picture of cardiac failure developed after pneumonectomy in individuals entirely free of myocardial damage, arteriosclerotic heart disease, valvular disease, or without clinical manifestations of acute anoxia. The precipitating causes are altogether obscure and the development of cardiac failure is unpredictable.

The return of hemorespiratory gas exchange to a normal state following pneumonectomy was studied experimentally by Heuer and Andrus.[15] On the basis of technics available at the time their studies were made, these authors concluded that proper adjustments in respiratory gas exchange, under resting conditions, in dogs may be delayed one month or more. In man, a study of the carbon dioxide content and the oxyhemoglobin saturation made in our clinic[2] revealed that in the absence of complications the state of respiratory gases in the arterial blood was normal within a few days after pneumonectomy. In addition, this study showed that following lobectomy some degree of anoxia persisted for longer periods of time, possibly as a result of inadequate correlation between alveolar ventilation and pulmonary circulation in the remaining lobe on the operated side, as it reexpanded slowly. A persistent arterial oxyhemoglobin unsaturation after pneumonectomy may be due to three causes: (1) The presence of a large bronchopleural fistula; (2) a state of distention or compression of the remaining lung brought about by mediastinal shift; and (3) development of pneumonia in the remaining lung. The additional risk of anoxia during a period, so fraught with other hazards, requires that the variation of oxyhemoglobin saturation in the arterial blood should be carefully followed.

The late effects of pneumonectomy upon pulmonary and cardiocirculatory functions have been studied in great detail in dogs, operated upon as puppies or adult animals.[4, 5] Recently these studies have to some extent been duplicated in children[1], and extended to adult man in the present report. In puppies and young children the surprising finding was that the capacity to perform exhausting exercise after pneumonectomy was comparable to that of the normal controls. In puppies, after pneumonectomy, there was enlargement of the remaining lung and histologic evidence of pulmonary hyperplasia. In young children hyperplasia was not demonstrated and the best performances were observed in those cases where the size of the remaining lung in forced expiration was not larger than predicted for one of a pair of normal lungs. The physiologic paradox of as good a performance with one lung as with two, under conditions of extreme physical demands, may be explained partly by the following considerations:

(1) Theoretically, it may be shown that the higher the ratio of tidal air to functional residual air, the more efficient is the mixing of gases in the alveoli. Such a situation arises after pneumonectomy: the dead space in the bronchial tree is reduced—the tidal air in one lung is larger, both combining to increase the efficient tidal air, and finally the functional residual air is smaller providing the remaining lung is not distended. (2) The tidal air is probably better distributed to ordinarily poorly ventilated lung areas, particularly around the hilum and at the apex, as the lung expands toward the opposite hemithorax in inspiration. (3) More blood circulates through the remaining lung as the functional diffusing surface for respiratory gas exchange is either increased in area by increase in the number of functioning capillaries or increased in efficiency by passage of more blood per unit of ventilated

alveoli. These considerations applying also to adults may well explain why respiratory gas exchange under conditions of moderate strain was efficiently managed in the younger group reported in the present paper.

In contrast to respiratory gas exchange ventilatory function is impaired in children and in adults after pneumonectomy. The breathing reserve under varying conditions of activity is lower than in normal subjects, and the tendency to dyspnea is greater. The reduction of ventilatory efficiency, however, is not proportional to the loss in lung volumes and to a considerable extent depends upon the degree of pulmonary distention.

The question of late development of pulmonary emphysema following pneumonectomy, performed during adult life, has not yet been settled because of lack of long follow-up. So far, our experience has been that when the mediastinum was maintained in its normal position, lung volume measurements failed to reveal evidence of developing emphysema. This situation, in humans, is entirely different from that encountered in dogs, where the distention of the remaining lung cannot be prevented. The shift of the mediastinum after pneumonectomy may be controlled by organization of the fluid in the empty hemithorax, by oleothorax, or by thoracoplasty. Our data tend to show that thoracoplasty does not reduce further the ventilatory function if measures are taken to keep the spine straight, and thus preserve the maximum expansion of the chest-bellows on the unoperated side. Postthoracoplasty scoliosis is highly detrimental to the efficiency of the chest-bellows mechanics, as has been demonstrated by previous work in tuberculous patients[7].

No mention has been made, so far, in this report of bronchospirometry, which permits separate estimation of ventilation and gas exchange in each lung. In two cases, with suppurative disease of the lung, this method was found to be of practical value in helping decide between limited and extensive lung resection.

SUMMARY

1. The effect of pneumonectomy upon pulmonary and cardiocirculatory function has been studied in 12 adult patients.

2. The following measurements have been made:

(a) Lung volumes and subdivisions.

(b) Maximum breathing capacity.

(c) Ventilation, breathing reserve, respiratory gas exchange, and state of the respiratory gases in the arterial blood, under basal conditions, during moderate exercise, and during the recovery period from moderate exercise.

(d) Venous pressure, circulation time, and vital capacity before, during, and following an infusion of 1500 cc. of a saline solution in 30 minutes.

3. Ten patients, studied after pneumonectomy, were divided into two groups according to age, and compared to normal controls. Two of these ten patients were again studied after a thoracoplasty had been completed, and

two additional patients, not studied after pneumonectomy, were studied only after thoracoplasty. Six of the ten patients, studied after pneumonectomy, had already been studied before operation.

4. The chief difference between patients after pneumonectomy and normal subjects was the reduction in their breathing reserve in various states of activity. This reduction caused by a decrease in maximum breathing capacity was greater in the older patients because of the cumulative effect of abnormal hyperventilation.

5. The decrease in maximum breathing capacity was not proportional to the loss of lung volume, and was greatly influenced by the state of distention of the remaining lung.

6. The late effects of pneumonectomy upon gas exchange in the lungs, the state of respiratory gases in the arterial blood, and the cardiocirculatory function were insignificant.

7. In two patients, age 53 and 63, respectively, distention of the remaining lung due to mediastinal shift was detrimental to hemorespiratory gas exchange, especially in the older patient who had pulmonary emphysema.

8. A supplemental thoracoplasty in four patients did not impair, further, the ventilatory function; and in some patients was of distinct benefit.

9. Overdistention of the remaining lung following pneumonectomy, insofar as it impairs the mechanics of the chest bellows, and reduces the efficiency of gas exchange, is physiologically undesirable.

We wish to thank, particularly, Drs. Herbert C. Maier and Richard L. Riley for their assistance and many helpful suggestions.

REFERENCES

[1] Lester, C. W., Cournand, A., and Riley, L. D.: Pulmonary Function after Pneumonectomy in Children. Jour. Thor. Surg. (In Press).

[2] Maier, H. C., Cournand, A.: Studies of the Arterial Oxygen Saturation in the Postoperative Period after Pulmonary Resection. Surgery (In Press).

[3] Bremer, J. L.: The Fate of the Remaining Lung Tissue after Lobectomy or Pneumonectomy. Jour. Thor. Surg., **6**, 336, 1937.

[4] (a) Longacre, J. J., Carter, B. N., and Quill, L. McG.: An Experimental Study of some of the Physiological Changes following Total Pneumonectomy. Jour. Thor. Surg., **6**, 237, 1937.

(b) Carter, B. N., Longacre, J. J., and Quill, L. McG.: A Study of the Changes in Cardiorespiratory Physiology following Total Pneumonectomy in Young Developing Animals. Jour. Thor. Surg., **7**, 326, 1938.

[5] Longacre, J. J., and Johansmann, R.: An Experimental Study of the Fate of the Remaining Lung following Total Pneumonectomy. Jour. Thor. Surg., **10**, 131, 1940.

[6] Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency. I. Discussion of a Physiological Classification and Presentation of Clinical Tests. Amer. Rev. Tuberculosis, **44**, 26, 1941.

[7] Cournand, A., and Richards, D. W., Jr.: Pulmonary Insufficiency. II. The Effects of Various Types of Collapse Therapy upon Cardiopulmonary Function. Amer. Rev. Tuberculosis, **44**, 123, 1941.

[8] Cournand, A., Richards, D. W., Jr., and Maier, H. C.: Pulmonary Insufficiency. III. Cases Demonstrating Advanced Cardiopulmonary Insufficiency following Artificial Pneumothorax and Thoracoplasty. Amer. Rev. Tuberculosis, **44**, 272, 1941.

[9] Kaltreider, N. L., Fray, W. W., and Hyde, H. W.: Effect of Age on Pulmonary Capacity and its Subdivisions. Amer. Rev. Tuberculosis, **37,** 662, 1938.

[10] Darling, R. C., Cournand, A., and Richards, D. W., Jr: Studies on the Intrapulmonary Mixture of Gases. III. An Open Circuit Method for Measuring Residual Capacity and its Subdivisions. Jour. Clin. Invest., **19,** 609, 1940.

[11] Cournand, A. Baldwin, E. deF., Darling, R. C., and Richards, D. W., Jr.,: Studies on Intrapulmonary Mixture of Gases. IV. The Significance of the Pulmonary Emptying Rate, and a Simplified Open Circuit Measurement of Residual Air. Jour. Clin. Invest., **20,** 681, 1941.

[12] Cournand, A., Richards, D. W., Jr., and Darling, R. C.: Graphic Tracings of Respiration in Study of Pulmonary Disease. Amer. Rev. Tuberculosis, **40,** 487, 1939.

[13] Caughey, J. L.: Effect of Rapid Infusion on Venous Pressure: A Test of Cardiac Reserve. Proc. Soc. Exper. Biol. & Med., **32,** 973, 1935.

[14] Richards, D. W., Jr., Caughey, J. L., Cournand, A., and Chamberlain, F. L.: Intravenous Saline Infusion as a Clinical Test for Right-heart and Left-heart Failure. Trans. Assn. Amer. Phys., **52,** 250, 1937.

[15] Heuer, G. J., and Andrus, W. deW.: The Alveolar and Blood Gas Changes following Pneumonectomy. Bull. Johns Hopkins Hosp., **33,** 130, 1922.

DISCUSSION.—DR. ANDRÉ COURNAND (New York): Physiologic studies after pneumonectomy in children show remarkable resemblance to the findings just reported by Dr. Berry in adults. I have studied, so far, with Drs. Charles W. Lester and R. L. Riley the cases of five children after successful completion of pneumonectomy and return to normal life. Two of the five children had a marked displacement of the mediastinum toward the operated side persisting after complete expiration. Lung volume measurements show that the residual air volume of the single remaining lung of those two children was about the same as the residual air volume of two lungs of normal control. This was in contrast to the other three children, with mediastinum maintained in normal position, where the residual air volume was about half that of the normal control. Permanent overdistention of the remaining lung in the former group was associated with a much greater decrease in efficiency of the chest bellows for air displacement as in the latter. This was conclusively shown by measurements of maximum breathing capacity. As we have previously shown, this measurement is the best means of estimating the breathing reserve which, in turn, is closely related to intensity and development of dyspnea. It was thus not surprising to find that the intensity and duration of dyspnea for varying degree of exertion were greater in the two children with permanent overdistention than in the three others. These five children, during the performance of an exhausting type of exercise, showed remarkable efficiency in supplying oxygen to the tissues and displacing carbon dioxide from the circulating blood. As a matter of fact, with one lung these children were able to perform as much exercise as normal controls of same size and age; their breathing reserve was still large enough to afford the required ventilation although at the expense of comfort, as shown by greater degree of dyspnea; and finally, their oxygen intake and carbon dioxide output were as large. These observations confirmed the following concepts: 1. That the breathing reserve in normal is well over and above any physiologic demand; 2. That the limit to exhausting exercise is not ventilation but circulation.

With Dr. H. C. Maier we have studied the state of respiratory gas in the arterial blood during the immediate postoperative period following pneumonectomy. This study revealed that the carbon dioxide content and the oxygen saturation in the arterial blood, in the absence of complication, returns to normal within a few days after pneumonectomy. This is in contrast with what is observed after lobectomy, where some degree of anoxia persists for a longer period of time, supposedly as a result of inadequate correlation between the ventilation and pulmonary circulation in the remaining lobe or lobes on the operative side.

Persistent arterial oxygen unsaturation after pneumonectomy recognizes three possible causes: First, the presence of a large bronchopleural fistula; second, a state of distention or compression of the remaining lung brought about by mediastinal shift; and third, the development of pneumonia in the remaining lung. The additional risk of anoxia during a period so fraught with other hazards requires that the variation of oxygen

saturation in the arterial blood should be carefully followed.

As to the late development of pulmonary emphysema after pneumonectomy in children or adults, we have not yet settled the question, because of lack of long-following, but, so far, our experience has been that when the mediastinum is maintained in its normal position we failed to see any evidence of developing emphysema.

In summary, we might state that overdistention of the remaining lung after pneumonectomy is not physiologically desirable, either in children, in adults, or in the older age-group. The teleologic concept, that the increase in size of the remaining lung to make up for the loss of the other lung, will bring about functional compensation, is not borne out by physiologic studies.

DR. EVARTS A. GRAHAM (St. Louis, Mo.): Those who have not been primarily interested in chest surgery perhaps do not realize that there has been a very great deal of discussion and uncertainty in the minds of those of us who have been confronted by these problems, as to whether or not measures should be taken permanently to obliterate the empty space which is left after the removal of a lung.

In my first case, which is just past the ninth anniversary—I know because my patient always calls me up on the fifth of April, and he called me up again this year to remind me—when I completed the operation I was alarmed at the huge empty space which remained, and I thought that the only thing to do was a thoracoplasty to obliterate it. Consequently, I at the same time removed seven ribs. The patient made an uneventful recovery, although I removed the remaining three ribs at a subsequent date, about three weeks after the operation. I was greatly impressed with the ease of the convalescence of the patient. In fact, I demonstrated him at a meeting of the Clinical Surgical Society, which met at St. Louis only about two weeks after his operation. He apparently had no dyspnea, and everything was going along very well.

Of course, this is a very radical procedure to add to the operation of pneumonectomy, and when Dr. Rienhoff announced that apparently it was not necessary to obliterate this space by thoracoplasty, my own ideas wavered considerably, and after doing several total pneumonectomies without the performance of thoracoplasty, I decided that probably Dr. Rienhoff was right. Since that time, however, my own mind has wavered a good deal back and forth.

I think that we thoracic surgeons ought to be very grateful to Dr. Cournand and Dr. Berry for these very fine studies which have been reported here this morning. These, in a sense, also tend to confirm observations that were reported before the Association of Thoracic Surgery by Longacre two years ago, in which, also, evidence was brought out that probably in the long run the patient who has had a pneumonectomy would fare better if he had the space completely obliterated by thoracoplasty.

Now, if however one attempted to add a thoracoplasty as an initial procedure to the operation of total pneumonectomy, in all probability the mortality of the operation would rise. In the early days, I undertook to compromise this measure somewhat by performing a thoracoplasty first, in some cases, followed by total pneumonectomy. That procedure I abandoned because for various reasons I do not think it is a wise one.

In the patients whom Dr. Berry recorded as carrying a permanent pneumothorax substituted by an oleothorax, that perhaps is an effective measure which might be satisfactory in patients who might otherwise be a poor risk for subsequent thoracoplasty. But after all, of course carrying a lot of oil around in the chest is carrying a foreign body, and oleothorax for tuberculosis has had a rather high proportion of unsatisfactory results, largely because it is a foreign body that is carried around.

Dr. Rienhoff, however, suggested some years ago, that it is not necessary, that a thoracoplasty be performed at the time of the operation. If it should seem necessary it can be done some time later, and I think that that is sound advice.

DR. FRANK B. BERRY (closing): I should like to thank Dr. Graham very much for his kindly discussion, and say that I agree completely with him about the dangers of oleothorax, and it was merely given to D.M. as a makeshift, as we still hesitate to undertake a thoracoplasty on him.

We have had two other patients lately in whom this question has arisen. One was the man for whom we did a pneumonectomy for intrabronchial tuberculosis. He has been hospitalized since 1024. That is a great handicap to overcome. Following his pneumonectomy, he still had many aches and pains. His chief complaint was difficulty

in swallowing, though we could not demonstrate anything by esophagograms. We finally suggested that perhaps it was due to distention of his other lung and some push or pull which we could not demonstrate. Following thoracoplasty, he has been completely relieved, notwithstanding relatively good functional studies all along. He is now inquiring about the chances of getting a job; so apparently from the purely subjective standpoint it was completely worth while.

Another is a man of sixty. Following his pneumonectomy, he decided the best way to put himself in shape was to forget all about hospitals and promptly built himself up to the ability to walk ten miles a day. Two years later, this winter, he came back to us with pneumonia, from which he recovered, and again he left the hospital. He came back a few weeks later with acute dyspnea, and was markedly cyanotic from a diffuse bronchitis. Since then, during his convalescence, he has had similar attacks—paroxysms with acute dyspnea. I became very much worried about the possibility of his overdistention and within the last week we put him through complete studies, only to find that at the end of two years his lung still is about in the midline, there is a very good diaphragmatic excursion, oxygen saturation of 95 per cent, and exceedingly good maximum breathing capacity. So we have decided that his trouble is due probably to a true bacterial asthma, coming on in paroxysms, and has nothing to do with overdistention of the remaining lung.

Now we have never undertaken a thoracoplasty on him, nor do we intend to as long as he maintains this position, which it seems likely he will, and he has filled the operated side of his chest, just as Dr. Rienhoff has suggested, with some sort of plug of fibrin and coagulated serum sufficient to hold his mediastinum in place. In view of these recent difficulties, we were very much astonished to find such very good functional response in the midst of these series of paroxysms.

A PRACTICAL CONSIDERATION OF OPEN PNEUMOTHORAX UNDER SODIUM EVIPAL, SODIUM PENTOTHAL, AND ETHER ANESTHESIA*

CARL A. MOYER, M.D., AND JOHN B. MCKITTRICK, M.D.

ANN ARBOR, MICH.

FROM THE DEPARTMENTS OF SURGERY AND PHYSIOLOGY, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.

THE CHANGES in breathing which are induced by the collapse of the lungs were first described comprehensively by Hering and Breuer,[6] and by Head.[5] Although the experiments that they performed were carried out upon rabbits, the alterations they observed in the character of respiration are similar to the changes in breathing that occur when open pneumothorax is induced in dogs and human beings. The alterations in the character of breathing are as follows: An initial dominance of inspiratory activity and a retardation of breathing; a subsequent equalization of inspiration and expiration and an acceleration of the rate; and, finally, in many instances, the dominance of the expiration and a slowing of the rate. The initial dominance of the inspiratory act is probably the result of the changes in vagal reflex activity that are brought about by the collapse of the lungs.[3] The subsequent changes in breathing that occur as the period of pneumothorax extends are dependent, to a large extent, upon the development of asphyxia.[3, 4]

In view of the number of penetrating wounds of the chest that are now being suffered, a study of the effects of anesthetic agents upon the respiratory phenomena that are associated with open pneumothorax seemed to be justified, especially since a definite possibility exists that the knowledge gained from the experiments could be employed in treating people who suffer chest injuries.

METHODS

The general equipment and procedures have been described previously.[1]

Pneumothorax was instituted by opening the side arm of a flanged cannula of ¾-inch bore. The cannula was inserted into the right chest through the periosteal bed of the fourth or fifth rib. The mediastinal pleurae were perforated; therefore, the opening of the cannula permitted the lungs to collapse quickly. The withdrawal of air through the side arm reexpanded the lungs. Ninety-five per cent alcohol was injected into the intercostal nerves that were available in the field of operation. This was done in order to prevent nociceptive stimuli, set up by the retention of the cannula in the chest wall, from modifying the breathing.

The animals were anesthetized with sodium evipal† (1 methyl 5 Δ′ cyclohexenyl 5 methyl barbiturate) 50 mg. per kilogram, sodium pentothal†

* Read before the American Surgical Association, Cleveland, Ohio, April 6–8, 1942.

† Evipal and pentothal are used throughout the remainder of the paper to designate the sodium salts of these barbiturates.

(ethyl (1-methylbutyl) thiobarbiturate) 25 mg. per kilogram, or "open drop" ether. During the preparation of the animals for the experiments, the anesthesia was maintained at moderately deep levels. Before the experi-

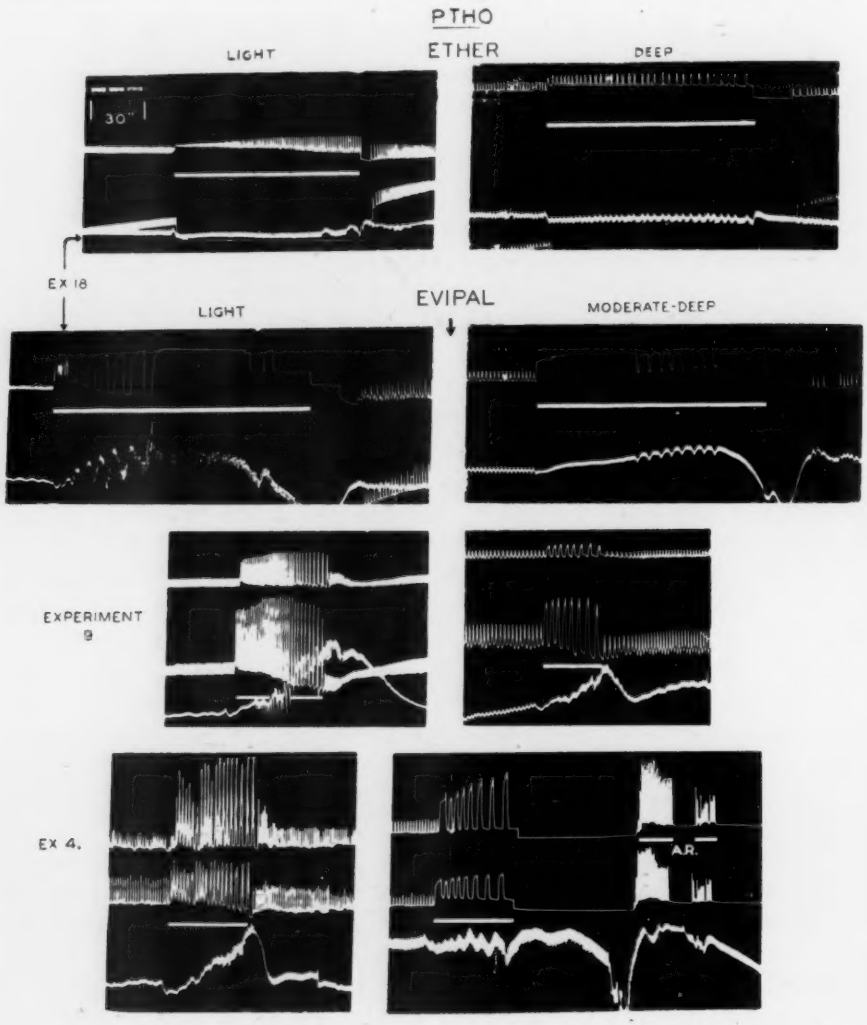


FIG. 1.—Illustrates the responses to open pneumothorax under light and deep anesthesia. Experiment 18 was begun with ether anesthesia and terminated with evipal anesthesia. Experiments 9 and 4 were conducted under evipal anesthesia.

mental procedures were begun, the anesthesia was regulated so that the corneal, the lid, and the patellar reflexes were very active, and the electrically excited, reflex contraction of the semitendinosis muscle relaxed slowly.

Three respiratory tracings were obtained: Tidal air (spirometer)*; chest breathing; and abdominal breathing. An inspiration was recorded as an

* The spirometer and chest tracings have been omitted in many of the illustrations in order to conserve space.

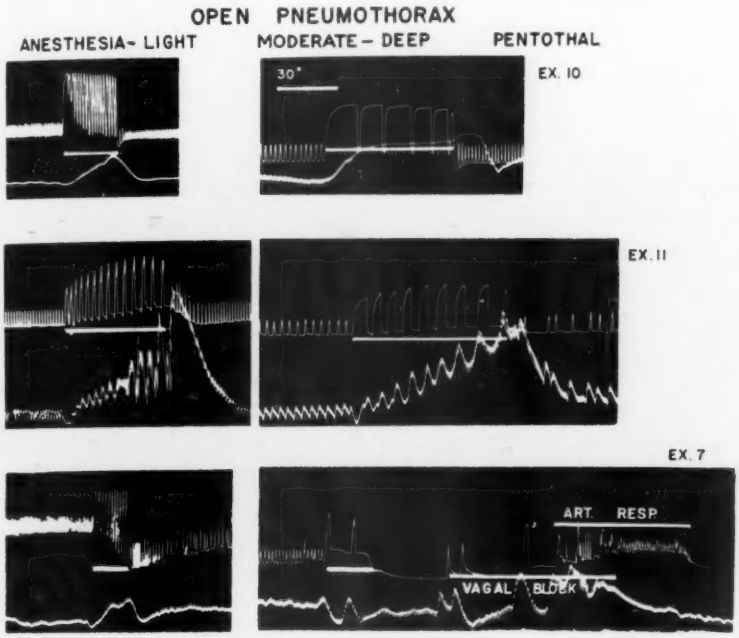


FIG. 2.—Illustrates the respiratory responses to open pneumothorax under light and deep pentothal anesthesia.

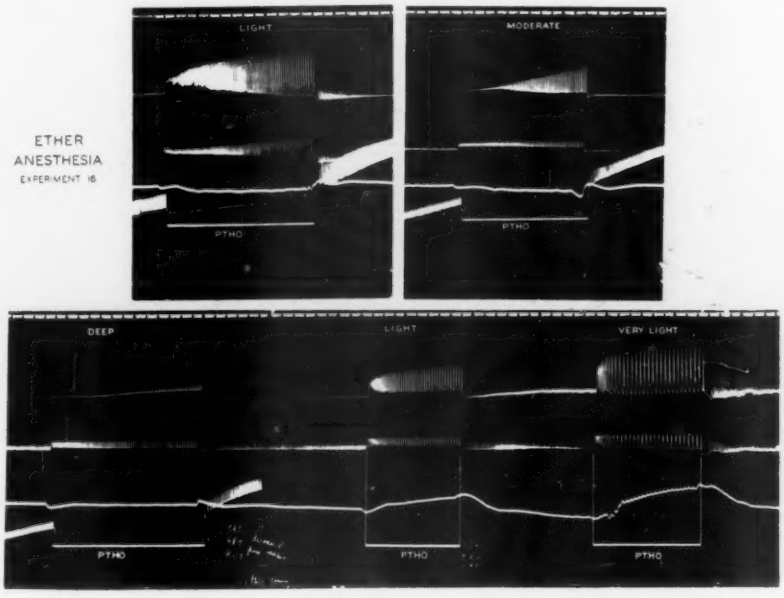


FIG. 3.—Illustrates the respiratory responses to open pneumothorax under light, moderate, and deep ether anesthesia. The rapidity with which the respiratory reactions change when the ether anesthesia is discontinued is shown in the lower record, within five minutes the response changes from that labeled "deep" to that labeled "very light."

upstroke on all of the records. A mercury manometer was used in recording the mean blood pressure in the femoral artery or in the carotid artery.

RESULTS

Twenty experiments were performed: Seven with evipal anesthesia, eight with pentothal anesthesia, and five with ether anesthesia. The types of the respiratory responses to open pneumothorax are illustrated in the first three figures (Fig. 1—evipal, Fig. 2—pentothal, Figs. 1 and 3—ether). During light pentothal, evipal or ether anesthesia the reactions of the animals to collapse of the lungs were similar. First, inspiration was intensified and prolonged. After the first respiratory cycle during pneumothorax had been completed, the prolongation of the inspiratory phase decreased and the intensity of the expiratory phase increased. These changes were associated with an increase in the rate of breathing. In many experiments the duration of expiration subsequently increased gradually and the respiration decreased in rate. (Fig. 1, Fig. 2—Exper. 11, and Fig. 3). After the lungs were reexpanded, a rate of breathing that was slower than the antecedent normal rate was present for varied periods of time.

During moderately deep anesthesia, open pneumothorax produced varied changes in the character of breathing. When evipal or pentothal were employed as anesthetics, three distinct types of reaction to the collapse of the lungs were apparent. One is characterized by a relative inspiratory apnea (Exper. 18, Fig. 1 (evipal), and Exper. 10, Fig. 2); another, by a fairly equal prolongation of the inspiratory and expiratory acts (Exper. 9, Fig. 1, and Exper. 11, Fig. 2); and the last, by a relative expiratory apnea, (Exper. 4, Fig. 1, and Exper. 7, Fig. 2). The type distribution of the experiments done with evipal and pentothal anesthesia is shown in Table I.

The institution of open pneumothorax during moderately deep ether anesthesia was followed by qualitatively similar reactions in all of the animals; the intensification and prolongation of the inspiratory phase is less, and the prolongation of the expiratory phase is greater than the respective reactions were when the anesthesia was light (Figs. 1 and 3).

The responses to reinflation of the lungs (the termination of the period of pneumothorax) were also variable when moderate to deep evipal or pentothal anesthesia was employed. In general, the animals placed in Group I (Table I) breathed more rapidly and more deeply, and those placed in Group II breathed more slowly and more deeply after the period of pneumothorax than they did before it. The animals in Group III were apneic after the lungs were reexpanded. Of the seven animals in Group III, three (two that were anesthetized with pentothal and one with evipal) failed to breath spontaneously after a brief period of lung collapse (30 seconds or less). Their breathing was eupneic before the pneumothorax was instituted. Intermittant artificial respiration was performed on these animals for 33 to 56 minutes. This maneuver succeeded in maintaining the mean blood pressure

of the animals above 130 Mm. as long as it was performed. However, an adequate spontaneous respiration was not reestablished. The other four animals in Group III recovered after the performance of artificial respiration or after the intratracheal administration of oxygen. Varied mechanisms are involved in the production and maintenance of the long postpneumothorax

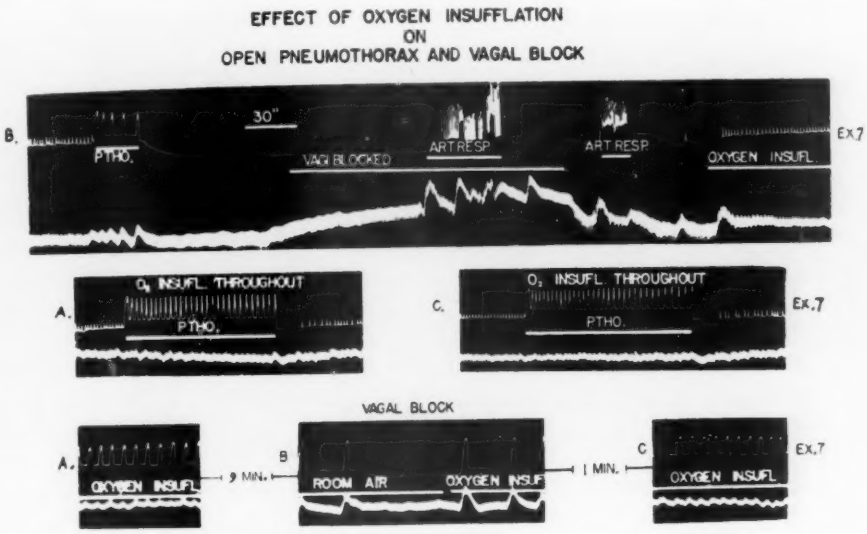


FIG. 4.—Illustrates the effect of the oxygen insufflation upon respiration during and after open pneumothorax, and upon respiration during bilateral cervical vagal cold block.

apneas. Asphyxia plays a very important rôle. If the asphyxia that frequently exists during moderately deep barbiturate anesthesia[1] is relieved and the development of the asphyxia that follows the collapse of the lungs is delayed or entirely stayed, by the intratracheal insufflation of air or oxygen, the long apneas do not occur (Fig. 4). The record A was obtained after

TABLE I

Anesthesia	Total Number	*Group I* Relative	*Group II* Balanced	*Group III* Relative
Moderate—Deep	of Animals	Inspiratory Apnea	Breathing	Expiratory Apnea
Sodium evipal	7	1	3	3
Sodium pentothal	8	2	2	4

the postpneumothorax apnea, illustrated in Fig. 2, Exper. 7, was broken by the intratracheal insufflation of oxygen. This oxygen insufflation was continued through A of Fig. 4. (Compare A of Fig. 4 with Exper. 7 of Fig. 2, and B of Fig. 4). Note the relative absence of expiratory dominance during the longer period of pneumothorax and the relative brevity of the postpneumothorax apnea when pneumothorax is instituted and stopped while oxygen is being insufflated, as compared with the response of the same animal when air is breathed before the pneumothorax, and the insufflation of oxygen is not employed. Note in Figure 4 B. that the long expiratory

postpneumothorax apnea was not successfully broken by artificial respiration but that it was very quickly relieved with the insufflation of oxygen. Part C of Figure 4 followed B. and the result is practically identical with that previously obtained under similar experimental conditions—Part A.

Although asphyxia produced great changes in breathing during and after

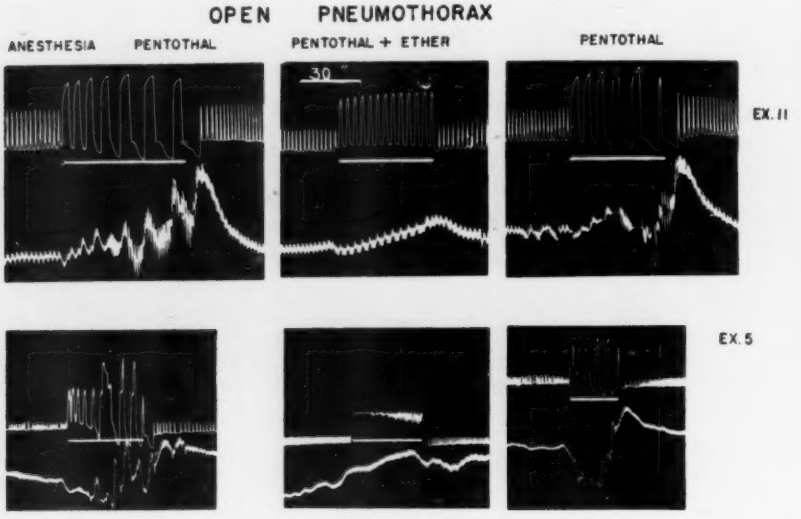


FIG. 5.—Illustrates the effect of ether upon the respiratory response to open pneumothorax under moderate pentothal anesthesia.

pneumothorax when evipal and pentothal are employed as anesthetics it does not produce similar changes in breathing when ether is used (Fig. 1, Exper. 18—ether, and Fig. 3). Not only is this apparent when the barbiturate and ether series are compared, but it is also seen in single experiments. The section of Figure 1, Exper. 18, that is labeled ether anesthesia, shows the respiratory reactions to pneumothorax under light and deep ether anesthesia; the section labeled evipal, immediately below it, shows the responses of the same animal to pneumothorax after evipal has been substituted for the ether (ether discontinued and evipal given when the ether anesthesia became too light). It is obvious that there is little similarity between the reactions during ether and evipal anesthesia.

Expiratory dominance during pneumothorax (anesthesia—evipal and pentothal) is entirely suppressed by a little ether vapor. Compare the sections of Experiments 11 and 5, in Figure 5, labeled pentothal, with those labeled pentothal + ether. Ether vapor was administered to the animals for five and nine minutes, respectively, between the first and second records, and it was discontinued between the second and third. No pentothal was given between the first and the third records.

Experiment 6, Figure 6, demonstrates the respiratory stimulating action of ether. Before ether was administered to the animal which was moderately anesthetized with pentothal, life had been maintained for 37 minutes by arti-

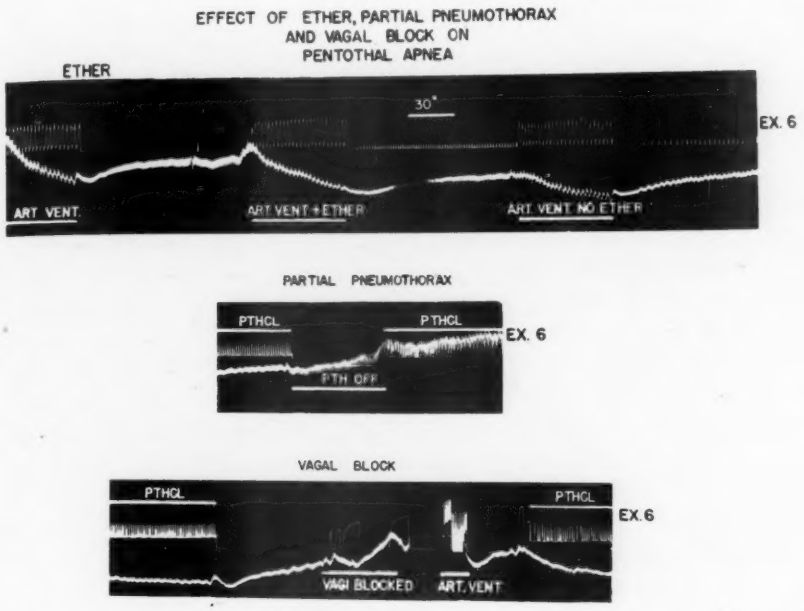


FIG. 6.—Illustrates the effects of ether, partial pneumothorax, and vagal block upon apneas that followed open pneumothorax under pentothal anesthesia.

ficial respiration after breathing had stopped following a short period of open pneumothorax. The administrations of ether for one and one-half minutes during a period of artificial respiration resulted in eupneic breathing that gradually faded out as the ether was blown off, and breathing finally stopped again. See the period below labeled "pth—off."

DISCUSSION

The type of anesthetic and the depth of anesthesia effect great changes in the characteristics of the respiratory response to collapse of the lungs. It is not surprising that the primary inspiratory stimulating effect of pneumothorax is less when the animals are anesthetized with ether than it is when they are anesthetized with evipal or pentothal, for ether has a comparatively greater depressing action upon reflexes than these barbiturates have.[2] (The inspiratory stimulating action of lung collapse has a reflex origin).[3]

The development of either inspiratory (very rare) or of expiratory dominance (common) during pneumothorax in many of the experiments conducted at moderately deep levels of evipal or pentothal anesthesia and the development of expiratory dominance during pneumothorax in all of the experiments conducted at deep levels of ether anesthesia are probably the result of asphyxia; however, the mechanisms involved in their production appear to be different. The characteristics of the expiratory dominance under evipal or pentothal anesthesia indicate that it is due to a relative overactivity on the expiratory center. (Consult reference 3 for a detailed discussion).

Two of five animals, when they were very lightly anesthetized with

ether, showed a small expiratory dominance of the overactive type (Fig. 3). However, the characteristics of the expiratory dominance that develops during the period of pneumothorax when the animals are deeply anesthetized with ether, indicate that this dominance probably is due to the depression of breathing by asphyxia rather than to a selective stimulation of the respiratory center. These characteristics are the gradual onset and the even increase, the paucity of evidence for an increased strength of expiration, the even and gradual recovery that follows reexpansion of the lungs, the absence of qualitative variations in the responses of different animals, and the striking similarity that the dominance bears to the respiratory depression effected by anoxia in animals deeply anesthetized with ether.[2]

The development of a strong expiratory dominance of the overactive type predisposes the animals to long apneas when the lungs are reexpanded. Apneas that are of sufficient length to necessitate the use of artificial respiration to maintain life did not occur in the experiments in which an inspiratory dominance (Exper. 18, Fig. 1—evipal; Exper. 10, Fig. 2), or a balanced breathing (Exper. 9, Fig. 1; Exper. 11 Fig. 2) obtained during the period of pneumothorax. Expiratory dominance of the depressive type (deep ether —Exper. 18, Fig. 1, and Exper. 16, Fig 3) did not predispose to long apneas in this series of experiments. No apneas of sufficient length to necessitate the use of artificial respiration were encountered during ether anesthesia. However, long apneas can undoubtedly be induced in animals deeply anesthetized with ether if the period of pneumothorax is extended enough to effect an asphyxial depression of the center to such a degree that spontaneous recovery becomes improbable.

Many factors appear to be involved in the institution and the maintenance of the apneas that follow open pneumothorax. The withdrawal of the intrathoracic air, that terminates the period of pneumothorax, rapidly increases the volume of the lungs; this increase in volume stimulates expiration. If the Hering-Breuer reflexes are active, as they usually are, in animals anesthetized with evipal or pentothal, the expiratory stimulating effect of inflation of the lungs will tend to reinforce the expiratory dominance developed during the pneumothorax. Although this mechanism very likely plays some part in the institution of the apneas, it is not of primary importance because the postpneumothorax apneas occur when pneumothorax is instituted after the afferent pathways of the Hering-Breuer reflexes (the vagi) are blocked or cut.[4] Furthermore, an overactivity type of expiratory apnea develops without the institution of pneumothorax when the vagi are blocked and asphyxia develops as the result of a decreased pulmonary exchange (Fig. 4, bottom). Undoubtedly asphyxia is very important for the development and the maintenance of the apneas. If the onset of asphyxia during pneumothorax is stayed, the postpneumothorax apneas do not appear. (Compare A and C with B or Figure 4). However, the effectiveness of asphyxia in producing the apneas is dependent upon the type of anesthetic and the depth of anesthesia. Very long apneas did not occur at any depth

of ether anesthesia or at light levels of evipal or pentothal anesthesia.

Evipal and pentothal may effect either one or the other of two basic changes in the balance of the respiratory mechanisms that might account for the apneas: either they increase the activity of the expiratory center more than that of the inspiratory center, or they decrease the activity of the inspiratory center more than that of the expiratory center. The data provided by this series of experiments are inadequate to establish the validity of one or the other of the above possibilities, however, these experiments

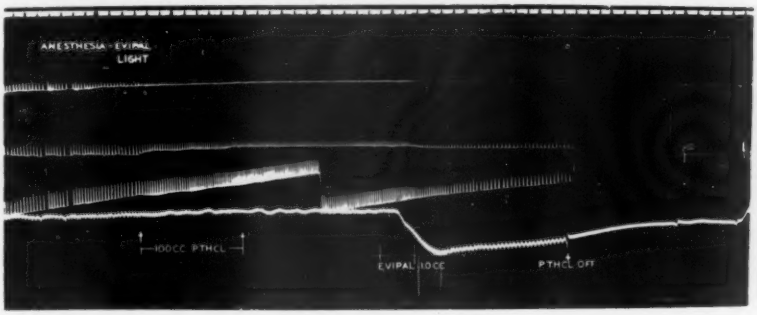


FIG. 7.—Illustrates the masking effect of a closed pneumothorax of 100 cc. upon the respiratory depression effected by evipal and pentothal. (This experiment was conducted under evipal anesthesia).

show that the apneas are easily broken by reflexly increasing inspiratory activity. The institution of the deflation Hering-Breuer reflex by admitting 150 cc. of air into the chest (pthcl.—closed pneumothorax) of an apneic animal institutes and maintains a eupneic breathing as shown in the beginning of the record in the middle of Figure 6. The withdrawal of the air (pth. off) stopped breathing. Reinstitution of the closed pneumothorax (150 cc.) reinstated breathing. The experiments demonstrate also that the administration of a small amount of ether to animals that are anesthetized with evipal or pentothal abolishes the expiratory dominance and breaks the apnea (Figs. 5 and 6, respectively). These actions of ether might be due solely to its reflex depressant action. This possibility is very unlikely since a great dissimilarity exists between the effects of vagal block and ether. (Vagal block rapidly and completely suppresses the transmission of respiratory afferent stimuli of pulmonary and vascular origin that traverse the vagi). Compare the records at the top and bottom of Figure 6. Therefore, it is probable that the effectiveness of small amounts of ether in suppressing expiratory dominance and in breaking the apneas is due to its respiratory stimulating action. Ether has been proven to be a very effective respiratory stimulant in rabbits deeply anesthetized with the long-acting barbiturates.[7]

Although the basic pharmocologic actions of evipal and pentothal which account for the disruption of breathing during and subsequent to pneumothorax have not been determined, it is apparent that the institution of a continuous inspiratory stimulation (closed pneumothorax), the administra-

tion of small amounts of ether, or the suppression of asphyxia (intratracheal insufflation of air or oxygen) will correct the disruption of respiratory balance.

However, in spite of the fact that effective measures can be taken to prevent and to overcome the dangerous respiratory phenomena which occur during and after pneumothorax when evipal and pentothal are used as general anesthetic agents, these barbiturates should be considered as being more dangerous than ether. Consequently, they should be employed with utmost caution as general anesthetic agents, especially when pneumothorax exists or will be produced.

Besides the apparent dangers that confront the breathing under barbiturate anesthesia, there are other factors that make evipal and pentothal more dangerous than ether, even in the most skilled hands. The most important of these factors is the relative lack of definitive signs of anesthesia during evipal and pentothal anesthesia. There are only two governing signs for barbiturate anesthesia, namely, the anesthesia is deep enough when the surgeon operates without signs of painful stimulation appearing in the patient, and the anesthesia is too deep when respiration ceases. There are no reliable signs available during adequate anesthesia to permit the anesthetist to ascertain the imminence of respiratory arrest until it does occur. Furthermore, the limiting sign—the cessation of breathing—is exceedingly variable. Painful stimuli, anoxia, and inspiratory stimulating proprioceptive respiratory stimuli mask overdosage.[1] The masking effect of a slight reduction in the volume of the lung is shown in Figure 7. Note that breathing increased when a 100 cc. closed pneumothorax was produced, that the rate of breathing decreased from 38 to 18 cycles per minute after one cubic centimeter of evipal was given, and that after a steady breathing had been established, breathing stopped when the pneumothorax was terminated. The "premortal" asphyxial rise of blood pressure is seen at the extreme right—breathing was reinstated by a 100 cc. pneumothorax; ten minutes later this was withdrawn and breathing stopped again. Forty-one minutes elapsed between the injection of evipal and the reestablishment of an adequate respiration without the stimulus of a small closed pneumothorax. Similar results were obtained in all of the experiments in which this procedure was performed (four with evipal, and three with pentothal). Therefore, the administration of evipal or pentothal, in the face of acute pneumothorax, must be done blindly and without assurance that breathing will continue after the operation is completed, the pneumothorax reduced, or the asphyxia, that is commonly associated with pneumothorax, is diminished.

In spite of the evidence that the barbiturates, in the presence of pneumothorax, are potentially more dangerous from the standpoint of breathing than ether, the experimental findings clearly indicate that pentothal could be safely and advantageously employed for the induction of ether anesthesia, especially in situations in which the gases ordinarily employed for this purpose are not available.

In circumstances that prohibit the use of ether, pentothal could be employed as a relatively safe anesthetic agent provided that the anesthetist and surgeon are cognizant of its limitations and the wide variations in breathing that frequently attend pentothal anesthesia.

Experiments recently performed indicate that hypercarbia (retention of carbon dioxide) rather than anoxia is the dominant component of asphyxia in the production of the disruptions in respiration that have been described. Therefore, increasing the oxygen content of the air inspired by the patient during the operation will not prevent these phenomena, because this expedient accelerates the development of hypercarbia when employed during pentothal anesthesia. The intratracheal insufflation of air or oxygen is the only measure that can be relied upon to prevent asphyxia or relieve it.

SUMMARY AND CONCLUSIONS

The respiratory responses associated with open pneumothorax in animals lightly anesthetized with evipal, pentothal, or ether were quantitatively similar. The responses of animals more deeply anesthetized with evipal and pentothal were varied; some were primarily inspiratory; some were balanced; others were primarily expiratory. The responses of animals more deeply anesthetized with ether were of the expiratory type. The inspiratory or expiratory dominance that is present or develops during pneumothorax in animals moderately anesthetized with evipal or pentothal is probably due to selective stimulation of the respective respiratory half centers and the expiratory dominance that develops during pneumothorax in animals deeply anesthetized with ether is probably due to depression of the center.

The presence of expiratory dominance during pneumothorax in animals anesthetized with evipal or pentothal predisposes to long postpneumothorax apneas. The development or expiratory dominance and of the postpneumothorax expiratory apneas is prevented by the intratracheal insufflation of air or oxygen or the administration of small amounts of ether.

The postpneumothorax apneas are broken by the intratracheal insufflation of air or oxygen, by a small amount of ether, or by a slight reduction in the volume of the lungs.

No postpneumothorax apneas were noted in animals that were anesthetized with ether.

A small closed pneumothorax masks the respiratory depressing action of evipal and pentothal.

Although, from a physiologic viewpoint, pentothal is less safe in the presence of pneumothorax than is ether, especially if asphyxia is present or develops, pentothal may be safely and advantageously employed to induce anesthesia that is to be maintained with ether, because ether effectively counteracts the untoward respiratory reactions seen under pentothal anesthesia.

BIBLIOGRAPHY

[1] Beecher, H. K., and Moyer, C. A.: Mechanisms of Respiratory Failure under Barbiturate Anesthesia (Evipal, Pentothal). J. Clin. Invest., **20**, 549, 1941.

[2] Beecher, H. K., and Moyer, C. A.: Unpublished data.
[3] Gesell, R., and Moyer, C. A.: Changes in the Balance of Respiratory Drives Resulting from Open Pneumothorax. Am. J. Physiol., **135,** 539, 1942.
[4] Gesell, R., Moyer, C. A., and McKittrick, J.: Some Special Instances of Predominant Chemical Stimulation of the Expiratory Half-Center. Am. J. Physiol., in press.
[5] Head, H.: Regulation of Respiration. J. Physiol., **10,** 1, 1889.
[6] Hering, E., and Breuer, J.: Die Selbsteuerung d. Athmung durch den Nervus Vagus. Litzgsber, Akad. Wiss., Wien, Math.-natur wiss. kl., **58,** (2 Abt.), 909, 1868.
[7] Klopstock, R.: Personal communication.

DISCUSSION.—DR. J. B. MCKITTRICK (Ann Arbor, Mich.): I would like to add a very brief word to what Dr. Moyer has already told you. It has to do with effects of high concentrations of oxygen and carbon dioxide in animals anesthetized with evipal and pentothal. This is pertinent to the pneumothorax problem, and is also important in dealing with patients anesthetized with these anesthetic agents for other conditions.

(Slide) These slides are set up exactly as those shown by Dr. Moyer, the upper line representing the exchange of air as measured by spirometer, the second line showing costal respiration, the third, blood pressure, and the lower line abdominal respiration. Throughout this period, represented by the base line, 100 per cent oxygen, is being administered, this animal having been anesthetized with evipal. During the administration of 100 per cent oxygen, respiration gradually slowed down until finally it ceased entirely. Various maneuvers were instituted to make these animals breathe again, namely, negative and positive pressure—that is, intrapulmonary pressure *via* the spirometer, and artificial respiration of the chest. Neither of these was successful. As soon as the 100 per cent oxygen was removed and the animal returned to room air, practically normal respiratory action ensued.

(Slide) If you will pay attention to this upper line and forget the rest, here again is an animal anesthetized with evipal. Sections A, B, and C represent increasing depth of anesthesia. The animal is given 12 per cent carbon dioxide and 28 per cent oxygen. Twenty-eight per cent oxygen functions to eliminate the stimulating factor of anoxia. You can see as the anesthetic depth is increased, the respiration again becomes progressively slower, and if the mixture is continued, will eventually cease.

It is only safe to inject a word of caution in using the common respiratory and resuscitative measures, namely, common dioxide and oxygen, in patients who have ceased to breathe under these anesthetic agents.

DR. FREDERICK A. COLLER (Ann Arbor, Mich.): I simply wish to state that my connection with this paper is due entirely to my interest in it, and the work was all done by Drs. Moyer and McKittrick.

I think the question might be raised whether at the present state of the practice of surgery a surgeon should any longer concern himself with these questions of anesthesia, or leave them in the hands of the anesthesiologist. My feeling is that there are as yet too few of them, and that we still must concern ourselves with the subject of anesthesia, because I find that when a patient dies under an anesthetic, I am the person who has to tell the family, so I still must take an interest in it.

There is one point I would like to emphasize, because it has seemed important and helpful to me, and that is that painful stimuli mask the depth of the anesthesia induced with the modalities we have been discussing. Last week we saw a most interesting case in a nearby town. Sodium pentothal was used for a very difficult bronchoscopic examination, and apparently there were difficulties to be overcome, and the anesthesia became deeper and deeper. Finally the procedure was over, the painful stimuli ceased, and the patient ceased to breathe, of course, because of the lack of the painful stimulation incident to the bronchoscopic examination. They gave the patient all the usual stimulants and, I think, several other things that happened to be on the shelf, without avail. Artificial respiration was then started, and 30 minutes later the patient began to breathe. Of course he was a decerebrate being from then on, and still is, due to this prolonged anoxia. Had they known enough to have given him ether and oxygen, as has been brought out in this paper, with forced respiration, the patient would have gone on to a successful convalescence.

I know that all of us have given many patients sodium pentothal without danger. I think, however, that we should know that many people do not have this good fortune. The man who gave this particular anesthetic, had only employed it six times previously. Upon inquiry we found two other instances where amateur anesthetists had a death rate

of about one in one hundred, which is too high. The deaths could all be averted had they known the advice given to us this morning. There is much that we still have to learn about anesthesia, and I believe a surgeon should have an up to date knowledge of all that is known.

DISCUSSION.—DR. EDWARD D. CHURCHILL (Boston, Mass.): There is one sentence in Dr. Moyer's paper which probably was too informal to be carried into the published version. I should like to have it appear in the discussion, namely: "Despite the fact that these animals were under the most careful scrutiny with a constant record of blood pressure, pulse, respiration, and objective signs for the depth of anesthesia." Dr. Moyer said, "Before we knew what was happening, we lost three animals under pentothal anesthesia."

TRANSTHORACIC RESECTION OF TUMORS OF THE ESOPHAGUS AND STOMACH*

EDWARD D. CHURCHILL, M.D., AND RICHARD H. SWEET, M.D.

BOSTON, MASS.

FROM THE SURGICAL SERVICE OF THE MASSACHUSETTS GENERAL HOSPITAL, BOSTON, MASS.

PART II

ABBREVIATED CASE REPORTS OF THE OPERATIONS WHICH FORMED THE BASIS FOR THE ARTICLE APPEARING IN THE ANNALS OF SURGERY, Vol. 15, No. 6, 897-920, June, 1942.

CASES OF CARCINOMA OF THE MIDTHORACIC ESOPHAGUS (ZONE II)

Case 1.—M. G. H., No. 162314: Female, age 43. Admitted 11/10/38. Epidermoid carcinoma, Grade III, at level of 7th dorsal vertebra. Obstructive symptoms one year. General nutrition good. No demonstrable metastases.

1/17/39—Jejunostomy. Upper abdomen not examined.

2/3/39—Transpleural esophagectomy (right side approach). Esophagus isolated in neck. Resection 4th rib and division 5th. Azygos vein divided. Esophagus sectioned four inches above cardia and distal stump inverted. Proximal esophagus and growth delivered through cervical incision.

3/20/39—Celiotomy. Esophageal stump delivered from mediastinum and brought to abdominal wall. Left gastric artery preserved.

4/20/39—Retracted lower stoma revised. Upper stoma revised.

7/19/39—First-stage skin-tube plastic.

10/13/39—Second-stage skin-tube plastic (Fig. 3).

3/28/40—Third-stage skin-tube plastic.

Result: Ingestion of semisolids and liquids. Delay at lower stoma required "milking" contents of antethoracic esophagus into stomach. Resumed activities as housewife on small farm.

12/17/40—Small left pleural effusion.

12/23/41—Bone metastases.

2/?/42—Died with disseminated metastases.

COMMENTS: Prolonged jejunostomy and stomal feedings caused weakness of muscles of deglutition, so patient had to "learn to swallow" after tube completed.

Lower stoma formed from esophagus produced delay in passage of food from tube to stomach.

Death in three years, from metastases, despite favorable operative findings and complete operation.

Case 2.—M. G. H., No. 179379: Female, age 63. Admitted 4/10/39. Epidermoid carcinoma, Grade III, at level of aortic arch. Substernal pain two months. No obstructive symptoms. General condition good. No demonstrable metastases.

5/5/39—Jejunostomy without exploration.

5/25/39—Transpleural esophagectomy (left side approach). Resection 5th rib. Growth, adherent to vertebral column behind aorta, was broken into during dissection.

* Read before the American Surgical Association, Cleveland, Ohio, April 6-8, 1942.

Removed, with two-inch margin above and below. Lower stump inverted. Proximal esophagus delivered through left cervical incision. An intercostal artery at aortic arch torn during dissection controlled by ligature. Catheter drainage of chest.

COMMENT: Acute mediastinitis from rupture of growth at operation aborted by sulfonamide therapy. Patient died 32 days after operation of hemorrhage from aortic point of origin of intercostal artery weakened by residual infection at former site of tumor.

Case 3.—M. G. H. No. 234193: Male, age 48. Admitted 2/5/40. Epidermoid carcinoma, Grade III, just below level of bifurcation of trachea. Dysphagia five months. No pain. Fifty pounds weight, loss; emaciated; anemic. Blood chemistry normal. No obvious metastases.

2/17/40—Jejunostomy without exploration. Transfusion.

3/27/40—Transpleural esophagectomy (right side approach). Resection 6th rib. Division 7th rib. Azygos and superior intercostal veins divided. Esophagus divided well below growth and distal stump inverted. Proximal esophagus and growth delivered through cervical incision. Left pleura opened during dissection. Closure impossible.

4/15/40—Exteriorization of distal stump of esophagus; esophageal hiatus sutured; left gastric vessels and vasa brevia divided. Biopsy of lymph node near left gastric vessels showed metastatic epidermoid carcinoma.

Result: Returned to work; ate liberal diet, using rubber tube connection. Developed stenosis of lower esophageal stoma.

1/15/41—Beck-Jianu gastrostomy. Lower stoma showed recurrence of carcinoma in esophageal wall.

6/6/41—Died, with metastases.

COMMENT: Use of esophagus distal to tumor in reconstructive procedure (1) invites disaster from inadequate removal of cancer; and (2) provides too small a stoma. Cases 1 and 3 led to substitution of Beck-Jianu gastrostomy as more acceptable procedure.

Case 4.—M. G. H. No. 220533: Male, age 53. Admitted 7/2/40. Epidermoid carcinoma, Grade II, in lower third of esophagus. Attacks of epigastric pain after eating. No vomiting. General condition and nutritional state good.

7/24/40—Jejunostomy with exploration. No abdominal metastases; left gastric nodes not involved.

8/3/40—Transpleural esophagectomy (left side approach). Resection 8th rib. Division ribs 7, 6, 5, 4. Growth not adherent. Esophagus divided 1½ inches above cardia and distal stump inverted. Right vagus nerve cut. Proximal esophagus and growth delivered through cervical incision; growth removed; proximal esophagus brought down through subcutaneous channel and out below clavicle. No drain.

9/6/40—Beck-Jianu gastrostomy; long tube; left gastric vessels and two upper vasa brevia cut.

Result: Excellent functional result, using a rubber tube connection. Gained 40 pounds.

6/22/41—Metastases in upper mediastinal lymph nodes.

9/?/41—Died with disseminated metastases.

Case 5.—M. G. H. No. 279893: Male, age 59. Admitted 12/11/40. Epidermoid carcinoma, Grade II, opposite aortic arch. Obstructive symptoms several months; substernal pain while eating for three weeks. Well nourished; good condition; no demonstrable metastases.

12/23/40—Beck-Jianu gastrostomy. No metastases to liver or subdiaphragmatic nodes.

1/9/41—Transpleural esophagectomy (left side approach). Intercostal incision, 8th

interspace. Posterior division of ribs 8, 7, and 6. Growth adherent to vertebral column; first upper right and two upper left intercostal arteries divided so as to retract aortic arch. Both vagus nerves cut. Lower esophageal stump inverted close to cardia; proximal esophagus and growth delivered through cervical incision; growth removed; proximal stoma brought out below clavicle.

6/7/41—First-stage skin-tube plastic using skin along right side of chest to be transplanted later to left side. Hairy chest.

9/3/41—Second-stage skin-tube plastic.

10/17/41—Third-stage skin-tube plastic.

Result: Developed pneumonia; finally showed evidence of recurrence. Died 4/24/42. (Reported in Table II as a surviving case.) Autopsy showed local recurrence in mediastinum with invasion of vertebral column.

COMMENT: Chest too hairy for use of skin between stomata. Rope-graft tube constructed from right lateral chest in hairless area, completed and ready for transfer to left side. Death from recurrence intervened before final stage was completed.

Case 6.—P. M. H. No. 40:1504: Admitted 9/30/40. Epidermoid carcinoma, Grade I, opposite aortic arch. Dysphagia four months. Poorly nourished; 30 pounds weight-loss. No demonstrable metastases.

10/15/40—Beck-Jianu gastrostomy. No abdominal metastases found.

11/4/40—Revision of gastrostomy; insertion of temporary rubber tube into lower end.

11/14/40—Transpleural esophagectomy (left side approach). Resection of 7th rib. Division of ribs 6, 5, and 4. Esophagus divided close to diaphragm; distal stump inverted. Upper two intercostal arteries divided to allow retraction of aortic arch. Proximal esophagus and growth delivered through cervical incision; growth removed; stoma established in neck because of high growth. Catheter drainage of chest.

12/23/40—Celiotomy. Gastrostomy closed. Distal esophageal stump pulled down. Left gastric and left gastro-epiploic vessels divided; entire upper half of stomach brought up in a subcutaneous channel in anterior chest wall and lower esophageal end brought out through a small incision opposite nipple.

4/14/41—First-stage skin-tube plastic.

6/5/41—Second-stage skin-tube plastic.

7/30/41—Celiotomy. Heineke-Mikulicz pyloroplasty to overcome persistent pylorospasm due to lack of vagus function and unopposed sympathetic action.

8/30/41—Third-stage skin-tube plastic.

Result: Remains well. Eats liberal diet of soft solid food. No delay in antethoracic esophagus. (See Figures 4 and 5 for photographs of completed external esophagus).

Case 7.—P. M. H. No. 41:900: Admitted 6/8/41. Adenocarcinoma arising in aberrant gastric mucosa, lower portion of middle half of esophagus. Dysphagia seven months. Twenty-five pounds weight-loss. General condition good.

6/20/41—Transpleural esophagectomy (left side approach). Resection 8th rib; division of ribs 7, 6, 5, 4. Growth too high for esophagogastrostomy. Esophagus divided at cardiac orifice. Inversion by suture. Proximal esophagus with growth delivered through cervical invision. Both vagi cut because of adherence to growth. Upper stoma brought out well below clavicle.

6/28/41—Beck-Jianu gastrostomy. Good swallowing ability by using rubber tube connection.

9/10/41—First-stage skin-tube plastic. Developed a virulent lobar pneumonia. Sulfathiazole treatment failed.

9/20/41—Died. Autopsy showed no evidence of malignant disease.

COMMENT: No preliminary gastrostomy in this case because it was thought

before operation to be one for resection followed by an esophagogastric anastomosis. The plan of operation had to be changed when the growth was found, on exploration, to be too high to allow an anastomosis to be done.

Case 8.—M. G. H. No. 37517: Male, age 72. Admitted 7/29/41. Epidermoid carcinoma, Grade III, opposite hilum of lung. Dysphagia one month. Ten pounds weight-loss. General condition exceptionally good for age. No demonstrable metastases.

8/18/41—Beck-Jianu gastrostomy. Long tube constructed. Upper abdomen explored; no metastases found.

9/8/41—Transpleural esophagectomy (left side approach). Resection 8th rib. Division ribs 7, 6, and 5. Tumor not adherent. Esophagus cut just above cardia; distal end inverted. Proximal esophagus with growth delivered through cervical incision; growth removed; proximal stoma two inches below clavicle.

Result: Remains well. Swallows with the aid of a rubber tube connection. Refuses skin tube.

COMMENT: One of two small nonadherent growths; both patients are alive and well (Cases 6 and 8).

Case 9.—P. M. H. No. 41:2016: Female 68. Admitted 12/11/41. Epidermoid carcinoma, Grade III, opposite 7th dorsal vertebra. Dysphagia five months. Marked emaciation and dehydration. No obvious metastases

12/27/41—Beck-Jianu gastrostomy. No metastases to liver or nodes below diaphragm. Remarkable improvement in general condition.

1/28/42—Transpleural esophagectomy. Growth densely adherent to left main bronchus and aorta. Posterior mediastinal vein torn; could not be secured without removal of esophagus. Esophagus divided below growth; lower stump inverted. Proximal esophagus delivered through cervical incision; growth removed; upper stoma below clavicle.

Result: Patient died on third day; cerebral thrombosis.

COMMENT: The accident of tearing a posterior mediastinal vein which could not be controlled without removing the growth forced completion of the operation. Without this the operation would have been abandoned because of fixation of the growth.

CASES OF TUMORS OF LOWER FOURTH OF ESOPHAGUS OR CARDIAC PORTION OF STOMACH (ZONE III)—TRANSTHORACIC APPROACH

Case 1.—M. G. H. No 212595: Male, age 59. Admitted 11/7/39. Adenocarcinoma, Grade II, involving cardiac portion of stomach and lower esophagus. Progressive dysphagia two years. Occasional hematemesis. General condition excellent. No anemia. Growth seen by esophagoscope.

11/12/39—Transthoracic partial gastrectomy with esophagogastric anastomosis. Resection 9th rib. Growth small. No evidence of metastases. End-to-side anastomosis, with silk. Catheter drainage of chest. Recovery uneventful.

Result: Remains well; works steadily. No functional difficulty now, but noticed regurgitation first few months especially while in dorsal recumbent position.

COMMENT: An unusually favorable case with no lymph node or other metastases. Good result could be anticipated.

Case 2.—M. G. H. No. 255165: Female, age 59. Admitted 6/15/40. Adenocarcinoma of the fundus of the stomach. Anorexia three months. Epigastric pain two weeks. Anemic; emaciated. Growth could not be seen through esophagoscope or gastroscope.

7/17/40—Transthoracic partial gastrectomy. Esophagogastric anastomosis; implan-

tation technic. Intercoastal incision 8th interspace. Growth large; lymph nodes around left gastric vessels involved; adherent; spleen removed with growth; phrenic nerve crushed. Catheter drainage.

Result: Recovery complicated by empyema. Died 11/8/40—bilateral pneumonia. No autopsy.

COMMENT: This is the only case in the series where the unsatisfactory method of implanting the end of the esophagus through a hole in the stomach wall, without layer suture, was used. Transitory leakage at the anatomosis was held responsible for the empyema.

Case 3.—P. M. H. No. 40:1549: Male, age 55. Admitted 10/8/40. Carcinoma of the fundus of the stomach involving the cardia. Dysphagia six months. Weight-loss, inanition, moderate anemia. Two preliminary transfusions.

10/15/40—Jejunostomy—Witzel method.

10/25/40—Transthoracic partial gastrectomy; esophagogastric anastomosis. Intercostal incision, 9th interspace. Division of 8th rib. Phrenic nerve crushed. Tumor large and adherent. Many lymph nodes involved. Careful layer suture, end-to-side, with silk. No drain. Uneventful recovery.

Result: Excellent immediate improvement. No swallowing difficulty. Gained weight. One year later, October, 1941, began to lose appetite, weight, and strength. Died two months later. Autopsy revealed extensive metastases to liver and abdomen; local recurrence as well.

COMMENT: Good palliation of one year's duration; size and fixation of growth plus lymph node metastases made cure improbable.

Case 4.—M. G. H. No. 270238. Male, age 40. Admitted 10/23/40. Carcinoma of entire upper two-thirds of stomach. Vomiting, anorexia, weight-loss; three months' duration. Emaciation; anemia. Gastroscopy failed to visualize tumor. Peritoneoscopy showed no metastases.

11/9/40—Transthoracic upper abdominal exploration. Large carcinoma invading retroperitoneal tissues; firmly fixed; inoperable.

Recovery uncomplicated. Discharged in two weeks. Died at home.

Case 5.—M. G. H. No. 273238: Male, age 68. Admitted 10/28/40. Adenocarcinoma of the cardiac portion of the stomach. Fatigue one year. Massive hematemesis, three weeks. Marked anemia; serum protein 4.9%; poor general condition. Polypoid growth seen by esophagoscope and gastroscope. Peritoneoscopy: No metastases seen. Transfused several times.

11/29/40—Transthoracic partial gastrectomy; esophagogastrostomy. Resection 9th rib. Large tumor, not adherent; nodes negative. End-to-side layer suture with silk. No drain. Phrenic nerve crushed.

12/17/40—Resection 6th rib left side for drainage of postoperative empyema. No fistula. Culture: *Staphylococcus aureas* and nonhemolytic streptococcus.

Result: Empyema healed promptly. Patient remains well. Swallows without difficulty. Roentgenograms show slight delay at pylorus.

COMMENT: One of three cases complicated by empyema.

Case 6.—M. G. H. No. 279061: Female, age 50. Admitted 11/27/40. Spindle cell sarcoma, fundus of stomach. One and one-half years of recurring hematemesis; fatigue; loss of strength. Mild anemia. Condition good. Tumor readily visualized through gastroscope.

12/11/40—Transthoracic excision of the tumor. Resection 9th rib. Phrenic nerve crushed. Tumor size of fist, in fundus. Local excision performed—fundusectomy. Silk.

Result: Recovery uncomplicated. Alive and well.

COMMENT: One of two cases of relatively benign tumors of the fibroma-

sarcoma group removed by local excision.

Case 7.—P. M. H. No. 40:1862: Male, age 62. Admitted 11/27/40. Adenocarcinoma of cardia and fundus. Infrascapular pain, anorexia, loss of weight, for two months. Emaciated; anemic. Peritoneoscopy showed the tumor; no metastases obvious.

12/18/40—Exploratory thoracoceliotomy. Resection 9th rib. Small amount of fluid in chest. Growth involved entire upper half of stomach and part of esophagus, firmly fixed posteriorly; many involved nodes; no other metastases. Deemed inoperable; chest closed. No drain.

Result: Prompt healing of wound. Patient discharged at end of three weeks to nursing home, where he subsequently died of his disease.

Case 8.—P. M. H. No. 41:100: Male, age 72. Admitted 1/22/41. Negative exploration. History of attacks of hiccough; epigastric distress and "dyspepsia." Well nourished; rather poor surgical risk. Roentgenograms showed apparent carcinoma at cardia. Esophagoscopic and gastroscopic examinations equivocal.

2/1/41—Transthoracic exploration of upper abdomen. No evidence of tumor or any other disease found.

Result: Recovery complicated by an attack of pulmonary edema. Discharged 15th day. Is living and well.

COMMENT: Esophagoscopic and gastroscopic examinations were inconclusive. Too much reliance was placed on two roentgenologic examinations, both of which were thought to show carcinoma.

Case 9.—M. G. H. No. 94953: Female, age 67. Admitted 1/28/41. Epidermoid carcinoma, Grade III, of lower esophagus just above cardia. Dysphagia, 4–5 months; anorexia; weight-loss. Emaciated; arteriosclerotic. No demonstrable evidence of metastases.

2/18/41—Transthoracic resection of lower esophagus and cardiac portion of stomach. Resection 9th rib. Lung very adherent; growth movable. End-to-side esophagogastric anastomosis; silk. Catheter drainage of chest.

Result: Recovery complicated by acute parotitis; otherwise normal. Good function of stoma. No stenosis (x-ray). Remains well, with no suggestions of recurrence.

COMMENT: Because of patient's age and history of carcinoma of sigmoid, resected in 1929, small margins of normal tissue above and below growth were allowed so as to make an anastomosis possible.

Case 10.—M. G. H. No. 294086: Admitted 3/21/41. Carcinoma of stomach invading lower esophagus. Gradually increasing dysphagia and weakness, one year. Anemic and poorly nourished.

4/2/41—Transthoracic total gastrectomy, splenectomy, and partial pancreatectomy. Resection 10th rib. Phrenic nerve crushed. No evidence of metastases. Growth large; involved almost entire stomach including abdominal esophagus; fixation to spleen and pancreas. Resection through lower esophagus and duodenum; spleen and tip of pancreas removed *en bloc* with stomach and adjacent lymph nodes. Duodenum inverted easily. End-to-side anastomosis of esophagus to upper jejunal loop; silk; two layers; jejunum suspended to crura of diaphragm; entero-enterostomy between two arms of jejunal loop. Catheter drainage of chest.

Result: Developed empyema and acute pericarditis. Autopsy revealed evidence of leakage at suture line.

COMMENT: The anastomosis was completed under too great tension.

Case 11.—M. G. H. No. 226834: Male, age 49. Admitted 4/24/41. Carcinoma of the cardiac portion of stomach involving the lower esophagus. Postprandial substernal pain, six months. Thin, emaciated. No demonstrable metastases. Esophagoscopy and gastroscopy revealed no evidence of tumor.

5/2/41—Jejunostomy for feeding. Upper abdomen explored. No metastases except to lymph nodes. Tumor surrounded cardia and involved abdominal portion of esophagus, extending to antrum on lesser curvature.

5/13/41—Transthoracic partial gastrectomy. Resection of 9th rib, division of 8th rib. Phrenic nerve crushed. Growth adherent to base of transverse mesocolon, part of which was excised. Large segment of stomach removed leaving greater curvature long. Esophagus divided 1 inch above level of diaphragm. End-to-side esophagogastric anastomosis, three layers, silk. Catheter drainage of chest.

Result: Uncomplicated convalescence. Functional result good. No stricture (x-ray). Transitory delay at pylorus lasting a few weeks. Remains alive and well.

Case 12.—M. G. H. No. 300779: Male, age 43. Admitted 5/21/41. Carcinoma of stomach (signet-ring type) involving lower esophagus and lesser curvature to pylorus. Epigastric pain ten months. Anorexia five weeks. General condition and state of nutrition good. No anemia. Growth seen by gastroscopy.

6/10/41—First stage of two-stage transthoracic gastrectomy. Proximal jejunal loop transected; end of distal portion inverted; proximal end anastomosed to the distal portion 12 inches below inverted end which was pushed into the lesser omental sac behind the stomach through an opening at the base of the transverse mesocolon. Catheter jejunostomy below anastomosis.

6/25/41—Transthoracic approach to stomach. Growth found too extensive to remove. Jejunal stump very adherent; tumor found in its mesentery. Operation abandoned.

Result: Uneventful recovery. Patient discharged home on 14th day.

Case 13.—P. M. H. No. 41:1050: Male, age 52. Admitted 6/26/41. Carcinoma of cardiac portion of stomach invading lower esophagus. Pain in left lower chest, two years. Occasional hematemesis, one year. Thin but in reasonably good condition. No demonstrable metastases.

7/7/41—Transthoracic subtotal gastrectomy. Resection 9th rib. Left chest negative. Phrenic nerve crushed. Growth not adherent. Esophagus sectioned 2½ inches above cardia. Stomach cut obliquely, removing lesser curvature but leaving greater curvature. End-to-side esophagogastric anastomosis, three layers, silk. Five grams sulfanilamide inserted in upper abdomen and five in left pleural cavity. No drain.

Result: Immediate recovery excellent. Next day developed auricular flutter which failed to respond to treatment; developed pulmonary and cerebral edema; died third day after operation.

COMMENT: No lymph nodes on specimen showed disease.

Case 14.—M. G. H. No. 318650: Male, age 44. Admitted 8/29/41. Adenocarcinoma of lower esophagus and cardiac orifice, Grade III. Substernal distress after deglutition, three months. Good state of nutrition. No demonstrable metastases.

9/17/41—Transthoracic resection of lower esophagus and cardia. Resection 9th rib. Phrenic nerve crushed. Esophagus divided two inches above growth; pathologist found tumor in cut edge; new level opposite inferior pulmonary vein chosen. Stomach cut across obliquely well below cardia; lymph nodes near left gastric artery removed. End-to-side esophagogastric anastomosis; two layers; silk. Four grams of sulfanilamide left near suture line. Catheter drainage of chest.

Result: Good early recovery. No leakage of suture line; excellent function with no stenosis. Developed small encapsulated empyema.

10/15/41—Rib resection for drainage of empyema. Uneventful recovery. Wounds healed. Remains well. Working.

COMMENT: This case illustrates the fact that there is often considerable growth of tumor in the submucosal and muscular coats of the esophageal wall and serves to emphasize the necessity for allowing a wide margin of

apparently normal tissue beyond the obvious edge of the tumor. (See also Case 3 of the Zone II series—midesophagus—where there was a recurrence of disease in the lower esophageal stoma).

Case 15.—M. G. H. No. 319590: Male, age 54. Admitted 9/4/41. Adenocarcinoma of lesser curvature and cardia invading lower esophagus, Grade III. Regurgitation of food, three months. Marked loss of weight. General condition fair; nutritional state depleted.

9/12/41—Transthoracic partial gastrectomy and splenectomy. Resection 10th rib. Phrenic nerve crushed. No metastases in chest or abdomen except lymph nodes near the growth which was large and adherent to the spleen. *En bloc* removal of spleen with upper half of stomach and lower two inches of esophagus. End-to-side esophagogastric anastomosis, two layers, silk. Four grams of sulfanilamide in chest. Catheter drainage.

Result: Good recovery. Uneventful convalescence. No complications. Function of anastomosis excellent; no stenosis (x-ray). Remains well.

RECENT EXPERIENCES WITH THROMBOPHLEBITIS OF THE LOWER EXTREMITY AND PULMONARY EMBOLISM*

THE VALUE OF VENOGRAPHY AS A DIAGNOSTIC AID

JACOB FINE, M.D., HOWARD A. FRANK, M.D.,
AND
ARNOLD STARR, M.D.
BOSTON, MASS.

FROM THE SURGICAL SERVICE, BETH ISRAEL HOSPITAL,
AND THE DEPT. OF SURGERY, HARVARD MEDICAL SCHOOL, BOSTON, MASS.

A STUDY OF STATISTICAL DATA in the recent literature on thrombophlebitis and pulmonary embolism shows (1) that approximately one of every 17 to 20 persons with clinically recognizable thrombophlebitis of the deep veins of the lower extremity will die of embolism, and (2) that one person of every 6 to 12 who have survived one or more attacks of embolism will die of a subsequent embolus,[1, 2, 3] Since the great majority of pulmonary emboli, except those of cardiac origin, have been shown to arise in the deep veins of the lower extremity,[4, 5, 6, 7, 8] a direct attack upon the site of origin is possible.

The use of heparin has certain obvious disadvantages. Since there are no reliable earmarks by which to identify individuals susceptible to thrombosis, the routine use of heparin for successful prophylaxis against thrombosis would make the trouble and expense involved prohibitive. Its use for prophylaxis against embolism in patients with recognizable thrombosis or with evidence of nonfatal embolism may have real value. But heparin will not dissolve a thrombus, so that when it is discontinued, a propagating clot may form at the site of the thrombus or a new thrombus may form (Cases 2 and 10, *vida infra*). There is no way of knowing when it may be discontinued safely. Bleeding or hematoma formation at the site of operation and elsewhere may result from its use.

Other effective technics are, therefore, urgently called for. Homans and, after him, several others[9, 10, 11, 12] divided the femoral vein as a prophylactic measure against embolism in isolated instances of thrombophlebitis of the lower leg. This procedure has not acquired the vogue which we believe it deserves. In a first series of patients so treated, we observed, in agreement with Homans, that (1) embolism did not occur, and (2) the phlebitic process in the leg subsided—in some instances at a remarkable rate. Pain decreased or disappeared in a day or two, and edema, when present, frequently began to subside more quickly than might be expected. The result was quite analogous to that obtained by novocain block of the paravertebral sympathetic trunk,[12] and was presumed to be due to a similar mechanism, *i.e.*, the breaking of a reflex arc producing vasospasm, with its undesirable sequelae.

Our experience with a second group of patients, who were studied with the aid of the venographic technic of Bauer,[13] is the subject of this report.

* Read before the American Surgical Association, Cleveland, Ohio, April 6–8, 1942.

VENOGRAPHY

The deep veins of the lower leg are readily filled by the slow injection, with a fine needle, of 20 cc. of a 35 per cent solution of diodrast* into the small subcutaneous vein constantly present on the lateral aspect of the ankle. Any good vein on the dorsum of the foot may serve if the superficial veins of the leg are partially occluded by a blood pressure cuff. The foot is elevated on a six-inch block, and an anteroposterior roentgenogram is taken at the termination of the injection (60 seconds), with the foot rotated

FIG. 1.—Case 1: The arrow indicates a probable minor filling defect, which, together with signs of deep phlebitis, led to division of the femoral vein.

internally to expose the widest space between the fibula and tibia. The deep veins of the lower leg and the lower third or half of the femoral vein will be visualized on a 14 x 17 film. Increasing experience has taught us the importance of visualizing the entire femoral vein, so that we now utilize a larger film. The pattern of the deep veins varies considerably in different individuals, but, in general, there are two main trunks joining to form the popliteal, which continues as the femoral into the groin (Fig. 11).

*We are grateful to the Winthrop Chemical Co. for a generous supply of this material.

A varying number of branches of the superficial system, including the perforators, also appear, and they are of much narrower diameter than the deep veins. Since thrombosis is frequently present in an apparently uninvolved side, bilateral venography is generally indicated.

Filling defects in veins are of two types: Those due to venospasm alone; and those due to partial or complete occlusion by thrombosis or clot. Presumably the two may coexist, but we have recently obtained evidence, to be presented elsewhere, that a uniform narrowing or a complete absence of filling of part or the whole of one or more venous trunks can be due to pure venospasm. A reliable differentiation between the two processes awaits the development of an effective and simple technic to relax venospasm during roentgenography, so that the diagnosis of thrombophlebitis will be possible on the basis of structural filling defects only. Until such a method becomes available, we believe it wise to regard all filling defects as evidence of thrombophlebitis if infarction has occurred or if the signs and symptoms are suggestive. The venographic evidence of thrombophlebitis presented in this paper should, therefore, be interpreted in the light of these considerations.

When deep phlebitis is present, the small vein at the ankle will be tense and distended if the phlebitic process is at all developed. Resistance to flow will then be encountered, and a varying degree of absence of filling of the deep veins will be observed in the film. In this situation the superficial veins will be more completely outlined. The veins in the groin and pelvis can be visualized by injection of the internal saphenous vein in the thigh with a 50 or 75 per cent solution of diodrast.

The circumstances in which the venogram serves a useful purpose are classified under five headings: (1) In thrombophlebitis of the lower leg, to observe the proximal limit of the propagating clot; (2) when, in the absence of local signs, a patient complains of pain in the legs before or after becoming ambulatory following operation or prolonged illness, to confirm or dispel the suspicion of phlebitis which should always arise; (3) in iliofemoral thrombophlebitis, to determine the proximal extension of the clot or thrombus; (4) in chronic ulcer of the lower leg, when the phlebitic origin of the ulcer is not assured; and (5) in varicose ulcer, to determine the location and number of incompetent perforators at its base and in superficial thrombophlebitis, to determine the presence of concurrent deep phlebitis. These conditions will be discussed in the order named.

A—THROMBOPHLEBITIS OF THE DEEP VEINS OF THE LOWER LEG

In a previous report[1] *routine* division of the femoral vein was recommended in *all* patients known to have or suspected of having thrombophlebitis of the deep veins of the lower leg. This conclusion was derived from the fact (1) that there was no reliable guidepost by which to predict whether or not an embolus would occur; (2) that the incidence, morbidity and mortality from emboli were far greater than is generally realized[7, 8, 14, 15, 16] Since a dependable venographic technic has become available, we no longer divide the femoral vein on the basis of suspicion, but *always* if the signs and

symptoms are obvious or if a filling defect is demonstrable in the venogram.

Examples of routine procedure are illustrated in the following six cases:

Case 1.—A female, age 32, one week after the birth of her second child, developed fever and pain in the right calf. The following day, examination showed tenderness in the right calf and fever persisted. There was no cyanosis, edema, ischemia or temperature change as compared with the opposite side. Venography showed a filling defect in one of the deep veins in the calf (Fig. 1). Immediate division of the common femoral vein was performed. Fever disappeared promptly thereafter; pain subsided on the 3rd postoperative day, and she was allowed out of bed. She remained symptom free. Four weeks later she showed only the faintest degree of ankle edema, which disappeared completely after eight weeks.

Comment: Although the venogram in this instance showed only a minor filling defect, the pain and tenderness were so outspoken as to leave no doubt of the diagnosis. We, therefore, regarded the risk of femoral vein division outweighed by the risk of embolus. The additional advantage of a short convalescence was a secondary consideration. According to Ochsner and DeBakey,[17] a shortened convalescence is also achieved by paravertebral novocain block, but this technic does not, we feel, provide protection against the discharge of an embolus.

Case 2.—A male, age 29, complained of pain in the right calf on the tenth day after repair of an umbilical hernia elsewhere. The pain increased in intensity, and on the 14th day it had spread to the groin. The entire leg was swollen. On the 15th day he developed cough, fever and pain in the left anterior chest. Intravenous heparin was given for four hours, twice daily, for seven days. The pulmonary signs cleared after five days of heparin therapy, but the leg remained painful for another 17 days. Swelling gradually subsided but recurred on the 36th postoperative day, when the patient got out of bed. He returned to bed at home for three weeks.

Two days after getting up, pain and swelling appeared in the *left* calf. He entered the Beth Israel Hospital three days later. On entry he had mild fever. Both lower legs were edematous, the left more than the right. The calf of the left leg was extremely tense and exquisitely tender on pressure, and Homans' sign was positive. There was no involvement of the veins of the thigh on the left side. Bilateral venography showed complete absence of filling of the deep veins of the lower legs. On the left side, the femoral vein was patent (Fig. 2). Accordingly, a diagnosis was made of subsiding thrombophlebitis of the deep veins of the entire right leg and acute thrombophlebitis of the deep veins of the left lower leg. The left common femoral vein, which was found to be free of clot or inflammation, was divided. Pain rapidly subsided, the tension in the calf decreased and the patient was able to walk on the 4th postoperative day. Within a week he was fully ambulatory, and swelling of the left leg decreased rapidly. Seven months later the left leg was normal. The right leg was still edematous; the right ankle showed degenerative changes in the skin; and an area of increased warmth was present in the lower third of this leg.

Comment: This patient had iliofemoral (and lower leg) thrombophlebitis on the right side. The impression that this condition does not involve a serious risk of embolism is not borne out in this and in other instances to which we shall refer later. The edema on the unoperated right side persisted

long after that on the operated left side, presumably because of the more widespread involvement of the veins on the right side. Heparin did not prevent the onset of thrombosis on the left side.

FIG. 2.—Case 2: A. Right venogram showing complete absence of filling of the deep veins of the lower leg. B. Left venogram. The deep veins of the lower leg are not filled, but the femoral vein is patent.

Case 3.—A male, age 36, complained of pain in the right shoulder and chest the day after removal of a plaster encasement, which had been applied to the left leg two weeks earlier for a fractured fifth metatarsal. He entered the hospital a week later, with a diagnosis of subsiding pulmonary infarct at the right base, and thrombophlebitis of the deep veins in the left lower leg. Examination revealed fever, a resolving consolidation in the right lower lobe and tenderness on pressure over the calf of the left leg which was very slightly swollen. Homans' sign was positive. Bilateral venography revealed normal veins on the right, but complete absence of filling of the deep veins on the left. The left femoral vein, exposed under local anesthesia, like the artery, developed a marked spasm. No clot or thrombus was present. The vein was divided between ligatures caudal to the entrance of the profunda. Tenderness rapidly disappeared. Chest pain subsided by the 4th postoperative day, when he was allowed out of bed. Slight edema of the lower half of left leg was present. He was discharged from the hospital on the 7th postoperative day, capable of normal activity. Four months later the leg looked entirely normal.

Comment: The undue persistence of pain and edema after sprains and fractures of the lower extremity will not infrequently be shown by venography to be due to phlebitis of the deep veins. The relatively high incidence of pulmonary embolism in major fractures of the lower extremities makes it worth while to have particular regard for signs of phlebitis in all such individuals.

Case 4.—A female, age 44, diabetic, complained of tenderness in the right calf three days after a panhysterectomy and bilateral salpingo-oophorectomy. Homans' sign was positive. A right venogram was interpreted as showing early thrombosis without complete occlusion of the lumen. The right femoral vein was immediately divided below the entrance of the saphenous vein. No inflammatory process was present in or

FIG. 3.

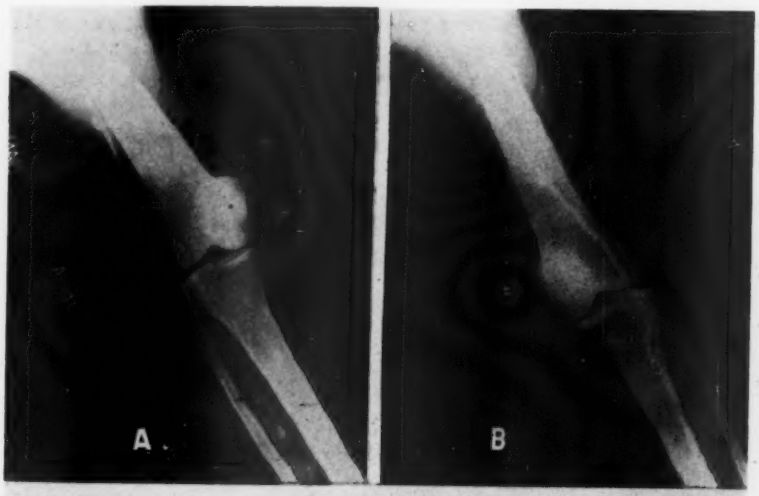


FIG. 4.

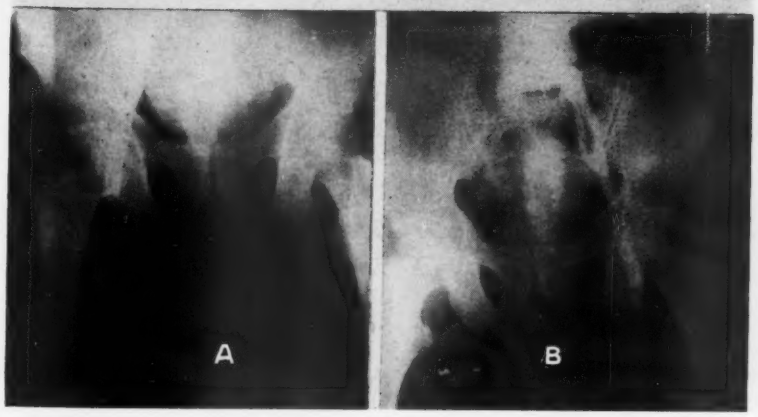


FIG. 3.—Case 5: A. Right venogram. Incomplete filling of deep veins of leg. B. Left venogram. Absence of filling of deep veins of lower leg. Femoral vein fills normally.

FIG. 4.—Case 5: Normal filling of the iliac veins nine days after division of both common femoral veins.

near these structures and the lumen of the vein did not contain a clot. Edema of the ankle appeared and persisted, and some pain continued in the right leg. She was discharged ten days after division of the vein. Five months later she had edema only if she walked without an elastic support. She had slight pain and tenderness, just below the inner aspect of the knee, which was probably due to foot strain.

Case 5.—A male, age 75, with generalized arteriosclerosis, hypertension and pulmonary emphysema, was out of bed on the 7th day after the second stage of a supra-

pubic prostatectomy. He started to walk on the 12th postoperative day. That evening the white blood count rose to 14,000. The next afternoon he became dyspneic, felt pain in the chest and showed congestion and multiple areas of increased density in the lower lung fields. Infarction was suspected. There was edema of both legs, more on the right, and moderate tenderness of the right calf. Bilateral venograms showed incomplete filling of the deep veins of both lower legs (Fig. 3). Bilateral common femoral vein division was done the same evening. No clot was found at the level of division. The next morning he felt better, and became afebrile. The dyspnea, chest pain and tenderness in the right calf disappeared. He was out of bed on the second day after vein division. At the time of discharge the edema was much less than at the time of vein division. Bilateral pelvic venograms were taken through the saphenous vein, nine days after division of the common femoral veins. These showed normal filling above the site of division (Fig. 4).

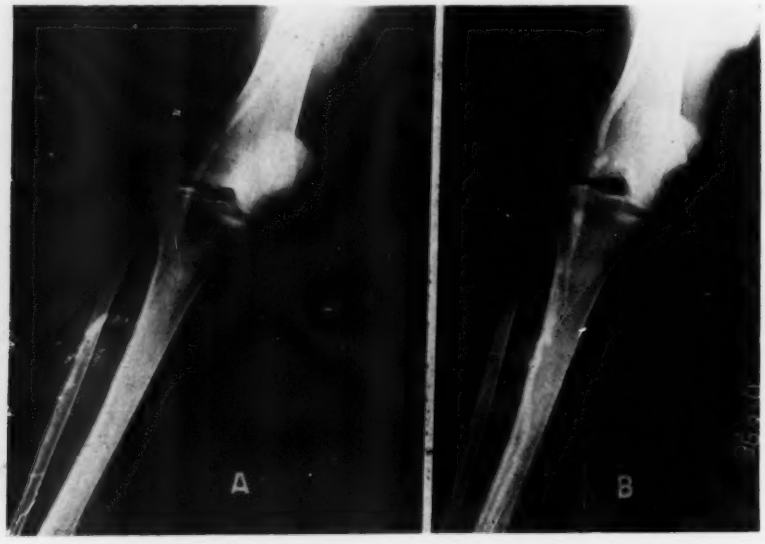


FIG. 5.—Case 6: Bilateral incomplete filling of deep veins of the lower leg: Both femoral veins are well outlined.

Case 6.—A male, age 58, was ambulatory on the 17th day after a perineal prostatectomy. On the 19th day he complained of bilateral calf pain. Homans' sign was positive in the left leg, the calf of which was tender on pressure. No other signs of thrombophlebitis were observed. Venography was recommended but was not done until two days later, when, shortly after getting out of bed, the calf pain increased on both sides. The venograms showed bilateral lower leg thrombophlebitis (Fig. 5). The following day the patient developed fever and pleuritic pain in the lower right chest, which showed râles and bronchial breathing. A roentgenogram showed infarction of the right lower lobe. That evening both common femoral veins were exposed under local anesthesia. They were free of clot or inflammation, and were divided between ligatures. Five days later the fever disappeared, and seven days later, when he was allowed out of bed, a roentgenogram of the chest showed almost complete clearing of the lung. Edema of both legs increased and reached a maximum after six months, at which time the patient reported that he had no complaints except a slightly heavy feeling in both legs.

Comment: The increase in the edema after division of the femoral vein was probably due to postoperative increase in the extent of the thrombosis. That it may have been due to failure to interrupt the vasospastic reflex arc is possible.

The existence of a vasospastic reflex arc, which is broken by the operative procedure, is strongly suggested by the lessening or complete disappearance of edema in most instances of thrombophlebitis in the deep veins shortly after division of the femoral vein. The promptness with which it occurs has led us, as well as Homans,[9] and Welch and Faxon,[10] to perform ligation of the saphenous vein in the fossa ovalis for painful phlebitis of the superficial system, with gratifying results in nearly every instance. In two patients who had extensive thrombophlebitis of the saphenous vein, with pain and swelling unabated for four and eight weeks of bed rest, respectively, division of the vein in the groin resulted in prompt relief of symptoms and restoration to full activity within three days. Two other patients after a week of continuous pain below and above the knee from an acute phlebitis of the internal saphenous were up and walking in entire comfort on the day after division of the vein in the groin.

FIG. 6.—Case 8: A. Right venogram. There is questionable normal filling of the deep veins of the lower leg. B. Left venogram. The deep veins of the lower leg do not fill.

Formerly, we regarded division of the femoral vein below preferable to division above the vena profunda, because the latter was regarded as a large, useful collateral for venous return. We now consider the common femoral the more desirable site for the following reasons: (1) A substantial number of thromboses occur in the profunda system; (2) the evidence for thrombosis in this system is not readily detectable clinically, or even with the aid of venography, except when the thrombosis is found at operation to have reached the mouth of the vein; and (3) significant postoperative edema cannot be shown to result from division of the femoral vein at any level, while division at the higher level is technically easier to perform.

The danger of overlooking the vena profunda is illustrated in the following cases:

Case 7.—A male, age 53, was subjected to laminectomy for removal of an epidural fat pad compressing the spinal cord. Among other symptoms he had anesthesia to pain in the inner aspect of the thighs and lower abdomen. On the 4th postoperative day the temperature rose to 102° F. Examination of the lower legs for phlebitis was completely negative. Twenty hours later he suddenly became cyanotic and dyspneic, and death followed shortly thereafter. Postmorten examination revealed a massive

pulmonary embolus arising from the right vena profunda, which contained a thrombus extending proximally into the iliac veins. The deep system below the vena profunda was not involved.

FIG. 7.

FIG. 8.

FIG. 7.—Case 8: A. Deficient filling of one branch of the deep veins in the right lower leg. B. Normal venogram of the left iliac veins.

FIG. 8.—Case 8: A. The right iliac and femoral veins above the site of division of the latter are well filled. B. The arrow points to a filling defect in the left femoral vein above the site of division.

Case 8.—A male, age 60, had an uneventful convalescence following repair of a recurrent inguinal hernia until the 11th day, when he complained of pain and tenderness in the left calf. There was no swelling, fever or leukocytosis. He was allowed up in a chair two days later, although still complaining of left calf pain and tenderness. A positive Homans' sign was elicited. Venography showed a filling defect of the deep

veins below the femoral on the left side, a questionably normal pattern on the right side (Fig. 6). That night the patient experienced right chest pain and showed physical signs and roentgenographic evidence of pulmonary infarction. The next morning, the 14th postoperative day, the venogram of the left leg was repeated. The previous filling defect in the left leg was again disclosed, and the left femoral vein *below the profunda* was divided. No thrombus or clot was seen. Occasional hemoptysis and signs of pleural effusion developed during the following week and mild fever persisted, but he was allowed in a chair on the 9th day after vein division. On the 11th day he suffered an attack of severe chest pain and cyanosis. A venogram of the left common femoral and iliac vessels showed no filling defect, but partial thrombosis of one venous trunk in the right lower leg was found (Fig. 7), although there was no clinical evidence of phlebitis in this leg and the femoral vein filled well. The right femoral vein *below the profunda* was divided. No thrombus or clot was found at this level. The patient, however, continued ill with fever for 21 days, when he developed more fever, chest pain, dyspnea and signs consistent with a new pulmonary infarct. A normal iliofemoral vein, above the level of division on the right, was demonstrated by venography, but a filling defect in the left common femoral above the site of division was found (Fig. 8). Gradually recovery ensued. Painless swelling of the entire left leg appeared, but was not relieved by paravertebral novocain block. Seven months later he was back at work without disability, except for slight swelling of the left foot.

Comment: This is an instance of failure to prevent embolism after bilateral division of the femoral vein below the profunda. Extension of a clot from the latter vein into the iliofemoral vein may explain the failure to prevent embolism. In another case, not described here, we had a similar experience. It was subsequent to these cases that we abandoned division below in favor of division above the profunda. Nevertheless, in the following case embolism occurred following bilateral division of the common femoral vein:

Case 9.—A male, age 81, with coronary sclerosis, emphysema, severe secondary anemia, hypertension, an inguinal hernia, and a sigmoid carcinoma for 18 months, was submitted to cecostomy for acute obstruction of the colon. Immediate postoperative convalescence was satisfactory, but an unexplained vague discomfort in the chest and restlessness persisted. He was out of bed on the 7th postoperative day, but the chest discomfort and general debility did not improve. A week later there was clear evidence, confirmed by venograms, of bilateral lower leg thrombophlebitis. Bilateral division of the common femoral vein was done. These veins were free of clot or inflammation. Death followed 20 hours later. Autopsy revealed fresh antemortem clot above the site of vein division on the right side, and fresh antemortem clot below the site of vein division on both sides. In the deep veins of both lower legs a relatively old fibrosing thrombotic process was found. The lungs showed multiple old pulmonary emboli and a fresh antemortem clot straddling the primary division of each main pulmonary artery.

Comment: The presumption is that this patient succumbed to a final embolus from a fresh clot which had formed in the right iliac vein subsequent to division of the right common femoral.

Case 10.—(Quoted by permission of Dr. Louis Hermanson): A male, age 34, weighing 264 pounds, developed a bilateral lower lobe pulmonary complication the day after cholecystectomy for cholelithiasis. On the 4th day he felt vaguely uneasy in the chest and had right calf pain. A right venogram showed a filling defect of the deep veins up to the knee. The right femoral vein, which was free of clot or thrombus, was

divided below the profunda. Fever persisted, but he was allowed up on the 12th day. On the 15th day he went into collapse and showed the signs and symptoms of massive pulmonary embolus. A left venogram showed a filling defect of the deep veins up to the knee (Fig. 9). The left femoral vein, which was free of clot or thrombus, was divided above the profunda. Mild edema of both legs was now evident. Slight fever persisted, but he was allowed up again on the 26th day, when he had another massive pulmonary embolus, with collapse, cyanosis and fall in blood pressure. Heparin was started immediately. Venography showed a filling defect in the right iliac vein, and a normal left iliac vein. Ligation of the right iliac vein was recommended but refused. Heparin was continued for 19 days, until the 45th day, when it was discontinued, and he was again allowed out of bed. A third massive pulmonary embolus occurred two days later (47th day). At the same time, vasospastic arterial occlusion occurred in the right upper and lower extremities. Return of blood flow was satisfactory in the right upper extremity a week later, and the cold blue right leg improved after three paravertebral novocain injections.

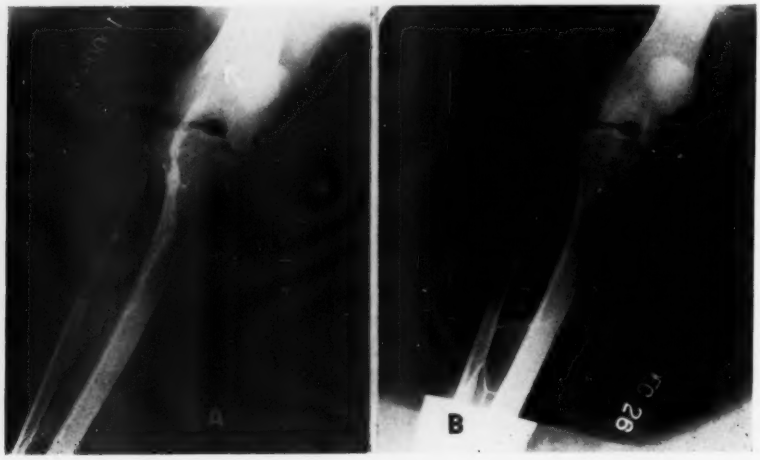


FIG. 9.—Case 10: A. The filling defect in the deep veins of the right leg involves the lower end of the femoral vein (at the arrow). B. The deep veins of the left leg do not fill.

After each attack of embolism fever rose to 104° F. Between attacks it varied from normal to 101° F. On the 63rd postoperative day, when fever increased, and râles in the right base and right pleural pain developed, venography of the iliac vessels was repeated. The left iliac vein showed a number of small filling defects, the right was not visualized owing to thrombosis of the right saphenous vein. The iliac veins were exposed transperitoneally. The left contained thrombus up to the entrance of the hypogastric vein, the right was surrounded by intense inflammatory reaction and was occluded by firm thrombus up to its junction with the vena cava. Both common iliac veins were ligated just below the inferior vena cava. He improved promptly, and continued to make a satisfactory convalescence.

Comment: It is evident from this and the previous case that femoral vein division cannot prevent thrombosis proximal to the site of division. This constitutes the chief limitation of this procedure for effectve prophylaxis against embolism. But since it is an uncommon occurrence, we feel justified in adhering to our position that routine division of the common femoral vein

is the procedure of choice in lower leg thrombophlebitis, unless, and until, two conditions can be satisfied: (1) That there is evidence that the act of division of the vein is, *per se*, responsible for the development of thrombosis proximal to the site of division; and (2) that paravertebral novocain block or heparinization, *after thrombosis has occurred*, can be shown to prevent embolism as often as vein division.

We must emphasize that we do not deny the great therapeutic importance of both heparin and novocain block. In appropriate circumstances each has indispensable value. For the prevention of embolism from lower leg thrombophlebitis, however, neither method should take precedence over division of the common femoral vein.

We are aware of the fact that the majority of such patients will eventually recover without surgical interference. Apart from the rapid rehabilitation which vein division achieves in most instances, deliberate failure to do so in any given instance is equivalent to deliberate acceptance of the risk of embolism in preference to the risk of division of the common femoral vein.*

The frequency with which wholly unsuspected pulmonary infarction or embolus has been found as the primary cause of death is evident from a number of sources. In three different series of routine autopsies, studied by McCartney,[18] Collins,[19] and Hunter, *et al.*,[7] pulmonary embolism was the primary cause of death in 2–3 per cent. In 3,500 routine autopsies, Hampton and Castleman[14] found pulmonary embolism the cause of death in 3–5 per cent, and pulmonary infarcts were present in 9 per cent. Belt[8] found pulmonary embolus the cause of death in 6 per cent of 567 routine autopsies. Ten per cent of these cases showed pulmonary infarcts. The two latter reports point out that the number of infarcts found depends on the care with which the search is made. Hampton and Castleman[14] found infarcts in 14 per cent of a carefully studied group of 370 autopsies. The discrepancy between the clinical and autopsy incidence of infarction is due to the widely divergent clinical pictures which infarction can produce. In our own experience, the roentgenologist, too, is frequently unable to distinguish between infarction and other pulmonary pathology.

The consequences of a hands-off policy in cases of lower leg thrombophlebitis have been described at some length by Fine and Sears,[1] but are worth illustrating by an additional experience:

Case 11.—(Quoted by permission of another hospital): A female, age 60, with a negative past history, except for slight dyspnea on exertion and a ligation of a varicose left saphenous vein a year previous, entered the hospital complaining of dyspnea, pain in the right chest and shoulder and pain in the left calf. She had been in bed at home for eight days before admission because of pain in the left calf, especially on walking. The lungs showed râles and bronchial breathing at the right base, and a

* Regardless of the condition of the patient, the morbidity and mortality of this operation in our hands has been *nil*, unless the development of thrombosis proximal to the site of division is regarded as a complication of the operation.

roentgenogram showed an infarct, presumably from phlebitis of the left lower leg. The process in the lungs cleared up completely shortly after admission. She became afebrile and apparently well. Toward the end of her stay the pain in the calf disappeared. A venogram showed a filling defect in the popliteal vein. Division of the femoral vein was considered, but an understandable difference of opinion as to the propriety of a relatively untried procedure led to a conservative management of the case. On the 15th day of her stay she was digitalized. She was allowed out of bed on the 17th day, when she suddenly went into collapse with cyanosis, fall in blood pressure and died in 30 minutes. Autopsy revealed a massive pulmonary embolus plugging the pulmonary conus. The heart was normal. No thrombus was found anywhere until dissection well down into the left thigh revealed a thrombus in the lower end of the femoral vein. The right leg veins were not involved.

There is a widespread, mistaken impression that pulmonary embolism is usually a postoperative complication, which is of no special concern to

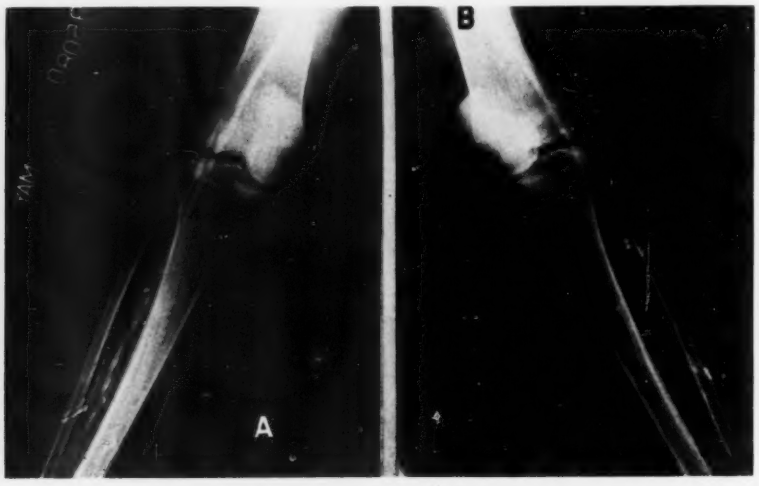


FIG. 10.—Case 12: A. The deep veins of the right leg filled normally. B. The deep veins of the left leg are narrow and one main trunk is apparently in spasm. The bones obscure one well filled trunk seen in the original film.

the practitioner or the internist. It is evident that thrombophlebitis of the deep veins of the lower leg is a common disease in nonsurgical patients, and occurs, not infrequently, in active, apparently healthy individuals. In Hampton and Castleman's series of 370 cases of pulmonary embolism and infarction only 40 per cent were postoperative, 30 per cent were of cardiac origin, and 30 per cent were neither. In Belt's series of 56 cases of embolism only 16 followed surgery, and 40 occurred in nonsurgical conditions. Similar evidence is available from other sources.[5, 6, 7, 15, 20, 21]

B—PAIN IN THE CALF ON FIRST BECOMING AMBULATORY AFTER OPERATION OR PROLONGED ILLNESS

This is a common complaint which is frequently ignored, especially when there are no concurrent objective signs to explain the cause of the pain. Occasionally such individuals succumb to a massive pulmonary embolus be-

fore or after leaving the hospital. The possibility of thrombophlebitis in the deep veins of the lower extremity should always be suspected and the diagnosis proved or excluded by doing a bilateral venogram.

Case 12.—A female, age 50, developed atelectasis in the right lower lobe two days after resection of the sigmoid for carcinoma. The process in the chest cleared by the 11th day. Abdominal wound sepsis also developed, but steadily improved, so that she was allowed up on the 18th postoperative day. Two days later she complained of pain in the left calf. Calf tenderness was minimal; there was no increased heat, edema or cyanosis, and Homans' sign was negative. Bilateral venograms showed no filling defect, but one main deep trunk on the left was much narrower than normal (Fig. 10). This might have been due to venospasm, which at this stage of our knowledge would not warrant division of the femoral vein. The subsequent course was uneventful.

Comment: In some six patients with a similar complaint the completely normal pattern of the veins allowed us to dismiss the suspicion of phlebitis and to discharge the patients. None developed phlebitis subsequently.

The decision for or against division of the femoral vein is occasionally difficult because minor filling defects in the venogram may be difficult to evaluate.

Case 13.—A female, age 65, developed fever and pain in the left upper quadrant and in both calves on the 5th day after a subtotal gastrectomy and splenectomy for a large gastric ulcer. Bilateral calf tenderness with no other accompanying signs of phlebitis was found. Venography disclosed a small filling defect in the lower end of one of the deep veins of the left leg. The hesitation to proceed in this instance was followed by disappearance of fever and calf pain within 24 hours.

Comment: When the signs and venographic evidence are minimal a decision to intervene may be difficult. Repeat venography, from day to day, can be done if necessary to fortify one's clinical judgment.

Occasionally a patient in bed with a protracted illness will complain of pain in one or both legs, which on examination seem to be entirely normal. A sensory neuritis due to a nutritional deficiency is commonly assumed, but thrombophlebitis may be present. Bilateral venography will establish or exclude this condition.

Case 14.—A male, age 27, returned to the hospital two months after resection of the ileum and cecum for regional ileitis. Extension of the disease to involve all of the colon as far as the sigmoid was found, and ileosigmoidostomy was performed. The postoperative course was marked by fever and diarrhea. Five days after operation he began having severe bilateral calf pain. Examination of the legs revealed nothing abnormal. The fear that he might develop a pulmonary embolus from a possible thrombophlebitis was allayed by obtaining the venogram shown in Figure 11.

C—ILIOFEMORAL THROMBOPHLEBITIS

In the foregoing discussion we were primarily concerned with the therapeutic problem in phlebitis confined to the veins distal to the common femoral and usually arising in the deep veins below the knee. So-called "primary iliofemoral thrombophlebitis" is generally regarded as less likely to result

in pulmonary embolism.[9] This, if true, is adequate justification to avoid surgical interference. The relative inaccessibility of the iliac veins is a sufficiently cogent deterrent as well. In addition to several cases already presented, our experience in a recent study of a small group of patients with iliofemoral thrombophlebitis leads us to question the notion that embolism is a rare complication of this condition.

Numerous attempts, including our own, to prevent embolism by the extraction of clots from these veins have been made with varying success.[9, 22, 23] This is to be expected—for removal of the clot may be incomplete, or, if the vein contains a thrombus, reformation and further extension may very well occur following extraction. Although iliofemoral and lower leg thrombophlebitis are identical in the pathologic sense,* the former constitutes a different therapeutic problem chiefly because of the anatomic approach and the surgical hazard involved in attempting to shut off the site of origin of the embolus.

When a diagnosis of thrombophlebitis of the lower extremity is made, the presence of tenderness in the groin or of edema of the thigh generally signifies the presence of clot or thrombus at least as far cephalad as the common femoral vein. Iliofemoral thrombophlebitis may, however, be present in the absence of edema of the thigh and in the absence of groin pain. Since the extent of involvement of the common femoral and iliac veins cannot be predicted with certainty, venography through the internal saphenous in the thigh to demonstrate the degree of patency is worthwhile. The prospect of a successful block above the site of the clot can thus be estimated. If the external iliac is involved, division or ligation above the clot or thrombus is possible. To accomplish this however is to undertake a procedure of major proportions. It may, therefore, not be advisable to attempt prophylaxis against embolism *routinely* by ligation or division in these individuals. Extraction of a loose clot *via* an opening in the common femoral vein is less hazardous, but less likely to be successful. However, since the threat of death from embolism exists, interference would seem to be justified. It was for this reason that we felt it worth while to explore the veins in the group of cases which follow:

Case 15.—A male, age 70, five days after suprapubic cystotomy for prostatic disease, developed congestive failure which improved with digitalis and quinidine. A roentgenogram on the 6th day showed an infarct in the right lower lobe. It was not accompanied by symptoms. On the 8th postoperative day the patient felt severe pain in the right calf, which was tender on pressure and showed thrombophlebitis in the short saphenous. The long saphenous was dilated and prominent. Venography showed complete absence of filling of the deep system of the entire leg, demonstrating the probable presence of iliofemoral thrombophlebitis (Fig 12A). From the right common

* The distinction between thrombophlebitis and phlebothrombosis made by Ochsner and DeBakey[17] is, in our view, one of degree rather than kind. So far as embolic complications are concerned, we can find no reliable distinguishing features which would allow us to judge when and when not to administer prophylactic measures.

femoral vein, exposed in the groin, a thrombus, 22 cm. in length, which included a valve from the mouth of the profunda, was extracted. The caudal half was red clot, the cephalic half was a firm white-gray thrombus. The common femoral vein was divided. Postoperatively, the right leg began to shrink, but the left leg began to swell. The next day calf pain and tenderness and a positive Homans' sign appeared in the left leg. The entire left leg was swollen and the left saphenous vein was distended. Ven-

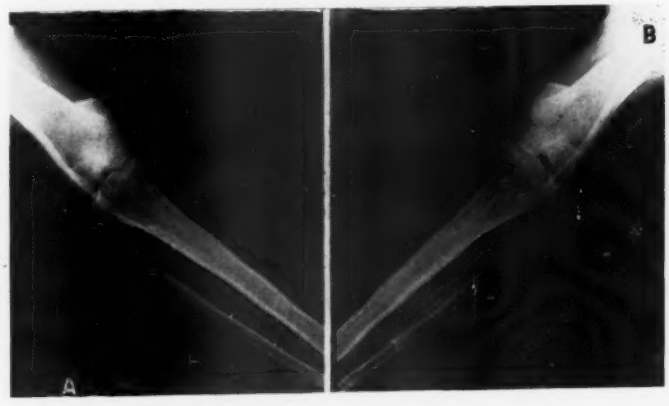


FIG. 11.—Case 14: Normal right and left venograms.

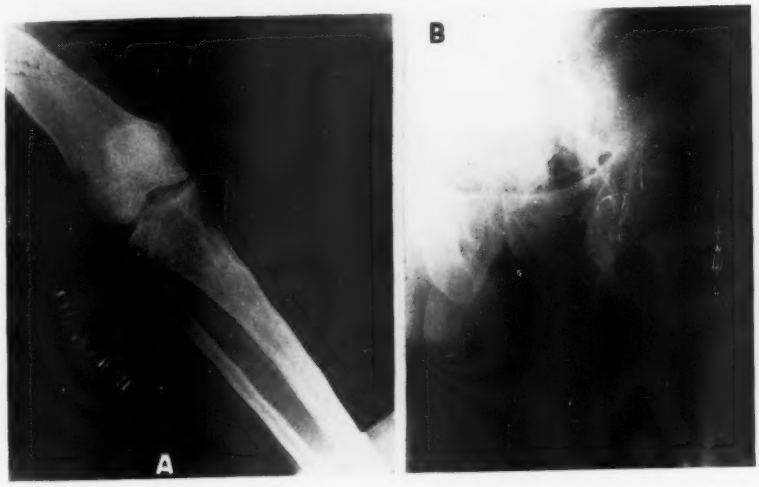


FIG. 12.—Case 15: A. The deep veins of the left leg do not fill. B. The left femoral and external iliac veins are dilated and partially filled with clot. Collateral venous channels are filled.

ography of the left common femoral and external iliac veins was done. This showed marked distention of the left common femoral vein, which seemed partially filled with clot extending into the external iliac (Fig. 12B). Collateral venous pathways were also visualized. Exposure of the left common femoral showed marked perivenous inflammation. Large clots and thrombi were removed from the left external iliac vein. The common femoral vein above the saphenous was ligated. Swelling of the left leg rapidly subsided. Two weeks later he was discharged free of edema in both legs, and when seen six weeks later the legs were normal. Venography showed a filling

defect in the right common femoral and external iliac veins, which was probably due to an organizing thrombus. On the left side venography was not done because the saphenous vein had been tied off and could not be used for injection.

Comment: In this patient the phlebitic process spread so rapidly, to involve the entire deep system, that one could not be certain where the process first began. The thrombus in the right femoral vein and the fresh red clot distally suggest that this may be an example of so-called "primary iliofemoral thrombophlebitis." It is possible, however, that a marked thrombophilic tendency can initiate the process in a number of areas simultaneously, with superimposed fresh clot extending in both directions. The pathologic studies of Neumann,[5] Rossslé,[6] and Hunter, *et al.*,[7] weigh the evidence in favor of the view that iliofemoral thrombophlebitis is in most instances a proximal extension of lower leg thrombophlebitis. In every case of iliofemoral thrombophlebitis which we studied by venography the deep veins in the lower leg were involved.

Case 16.—A male, age 20, complained of pain in the right calf 13 days after nephrolithotomy. He showed a positive Homans' sign. There was increased heat, fever and leukocytosis, but no edema. The calf was tender on pressure and there was tenderness in the groin also. A venogram showed defective filling of the deep veins in the lower leg. The femoral vein was not visualized. It was exposed under local anesthesia in the groin. No perivenous reaction was present, but the vein was filled with a loose fresh clot extending into the external iliac. The extracted clot was 10 cm. long. A few additional small clots were obtained by suction. The vein was then divided. Slight edema persisted for a week and on discharge the circumference of the right calf measured 0.5 cm. greater than the left.

Comment: It is debatable whether the thrombus began in the lower leg veins or the iliofemoral veins. It is impossible to claim that clot extraction avoided embolism, but it is fair to assume that the usual long convalescence which iliofemoral thrombophlebitis requires (*circa* 38 days for all types of thrombophlebitis[24]) was markedly shortened by this procedure.

Case 17.—A female, age 66, when allowed out of bed two weeks after cholecystectomy, complained of pain in the right lower leg and thigh. The calf and inner aspect of the thigh were tender on pressure. The superficial veins were varicose. There was slight cyanosis of the skin and swelling of the leg and thigh. Venography showed good filling of the superficial varicose veins, but the entire deep system failed to fill (Fig. 13). Exposure of the veins in the groin showed perivenous inflammation. The great saphenous, common femoral and external iliac, for an indeterminate distance proximally, were filled with fresh unattached clot. The common femoral and external iliac were evacuated until blood flowed from above. Troublesome hemorrhage from two tributaries entering the common femoral posteriorly was controlled by ligatures placed from within the lumen of the femoral vein, which was then obliterated by suture. Division was avoided for technical reasons.

On the day of operation the entire leg was swollen. Five days later calf tenderness disappeared and the superficial veins were no longer distended. Nine days later she was up and walking, and 12 days later, after gradual disappearance of all symptoms and signs except slight swelling of the lower leg on walking, she was discharged. Three

months later the right leg and ankle were still somewhat painful and mild edema of the ankle occurred on walking. There was slight right calf tenderness and the right leg was slightly warmer than the left.

Comment: Considerable bleeding in this patient makes it clear that the procedure of phlebotomy for clot extraction at this level can be a difficult one in certain circumstances.

In this instance the physical signs demonstrated involvement of the femoral vein and venography was not necessary for diagnosis. Nevertheless, even in obvious cases of phlebitis, venography is worth while, for it may reveal an extent of involvement not suspected from signs and symptoms alone.

Since the recovery of the preceding three patients was much more rapid than is ordinarily the case when conservative therapy is adopted, we believe that the operative procedure was beneficial. But two other patients with thrombophlebitis involving the entire deep system including the external iliac, from whose common femoral veins long thrombi were extracted, were not symptomatically improved. In one, the thrombus with superimposed clot was removed six hours after the diagnosis was made. Pronounced edema persisted for two months. In the other, pain and swelling continued for weeks afterwards.

Although, in the foregoing five cases, clot or thrombus extraction followed by division of the common femoral vein was not followed by embolus, the symptomatic relief achieved was satisfactory in only three. The claims made for heparin and for paravertebral novocain block, so far as symptomatic relief is concerned, are at least as good. Protection against embolism, however, is the factor of primary importance. For this purpose a comparative evaluation of all three methods is necessary. Perhaps a combination of methods may prove to be the best therapy.

Though we are on uncertain ground in deciding whether surgical intervention is justified before infarction has occurred, we should not hesitate to operate after a first infarct. To wait for a second infarct before operating, as Läwen,[22] and de Takats and Jesser[25] suggest, is too arbitrary a rule to be reliable. We regard a first infarct, however slight, a sufficient indication. The type of surgical procedure which should be adopted is by no means established. Läwen, Kulenkampff,[23] and de Takats and Jesser, limited their efforts to clot extraction without division of the vein. Our view is in agreement with that of Homans, that division or at least ligation should be done whether or not complete extraction of clot or thrombus is achieved. Should embolism occur after emptying and dividing the common femoral vein, we would not hesitate to ligate or divide the common iliac vein.

D—PHLEBITIC ULCER

Chronic lower leg ulcers may be assumed to be of phlebitic origin if a satisfactory history of deep phlebitis is obtainable. In some instances the history will be negative or equivocal. Accurate diagnosis and proper therapeu-

tic procedure will be facilitated if the exact status of the deep veins can be ascertained.

Case 18.—A male, age 58, entered the hospital for a chronic ulcer which had been present for eight years. It began some months after removal of an encasement applied for a fracture of the upper third of the tibia. On admission to the hospital examination showed massive edema from the knee to the ankle, cyanotic engorgement of the lower third of the leg and a weeping ulcer involving about a third of the anterior surface of the lower leg. No varicose veins were seen. The patient stated that these had been cured by ligation in the groin two years previously at another hospital. A venogram showed almost complete obliteration of the deep veins and absence of the greater saphenous system (Fig. 14). A nonvaricose, dilated lesser saphenous vein communicating with a venous trunk on the lateral aspect of the thigh was the sole remaining pathway for venous drainage. A diagnosis of phlebitic ulcer was assured and therapy applied accordingly.

FIG. 13.—Case 17: The deep veins do not fill. The superficial veins are varicose.

FIG. 14.—Case 18: The deep veins are almost entirely obliterated and the internal saphenous vein is obliterated. A lateral superficial trunk is the only significant venous trunk in the lower leg.

Comment: The obliteration of the internal saphenous system two years previously was ill-advised, for the venogram demonstrates that the ulcer was not a varicose ulcer and that the saphenous system was the only major channel remaining for venous drainage of the lower leg.

Venography provides a technic for correct orientation in stubborn or complicated cases of disease in the veins of the lower leg. The disastrous effects of therapeutic obliteration of dilated saphenous veins, which are mistakenly assumed to be varicose, but which in fact have developed to compensate for an obliterated deep system, will thus be avoided.

Whether the veins involved in deep phlebitis ever recanalize to a degree

sufficient to restore appreciable function, is an unsettled question for which venography will presumably provide an answer. In the case cited here recanalization has not and probably never will take place.

An extreme example of a presumably permanent obliteration of the deep system is the following:

Case 19. A female, age 48, obese, mother of seven children, entered the hospital because of epigastric, periumbilical and left-sided abdominal pain of six weeks duration. There were no associated gastro-intestinal signs or symptoms. She gave a history of three attacks of deep thrombophlebitis of the lower extremities, one of which, 13 years ago, after childbirth, was bilateral and very severe. Aside from obesity and hypertension, physical examination was negative except that the superficial veins of the lower left half of the abdominal wall were indurated, tender, and more prominent than usual. Superficial varices were observed in both lower extremities; those on the left were reddened and tender. The abdominal pain was attributed to phlebitis of the veins in the abdominal wall, probably including the veins in the falciform ligament. Venography of the lower extremity showed complete absence of the deep veins in the right leg and pelvis with gross dilatation of one collateral channel in the abdominal wall. On the left there was nearly complete obliteration of the deep system of the veins in the leg and pelvis, with numerous small collateral channels in the abdominal wall, some of which were presumably blocked by the active thrombophlebitis.

E—VARICOSE ULCER AND SAPHENOUS THROMBOPHLEBITIS

The venogram can be useful to locate the position and number of incompetent perforators in the bed of a varicose ulcer which persists following obliterative therapy of varicose saphenous veins.

We have already referred to the accelerated rate of recovery in superficial thrombophlebitis by division of the saphenous vein in the groin. The following is an instance of septic thrombophlebitis beginning in the saphenous system:

Case 20. A female, age 50, diabetic, was submitted to ligation of a varicose left internal saphenous vein in the groin. Wound sepsis followed and spread to the surrounding tissues, requiring multiple incisions. Repeated chills, fever and positive blood cultures established the diagnosis of *Staphylococcus albus* septicemia or pyemia, which did not subside in spite of adequate sulfathiazole and sulfadiazene therapy. Ligation of a vein containing the septic thrombus, which was considered responsible for the generalized infection, required a knowledge of the status of the deep veins. A venogram showed complete obliteration of the deep system in the lower leg. Since the infectious process began in the groin the deep veins at this level were presumably also involved. A venogram of the iliofemoral veins could not be taken because of the obliteration of the saphenous system. It was obvious that nothing could be accomplished by an approach below the inguinal ligament. The left iliac vein was exposed through an extraperitoneal incision, and the proximal end of the thrombus was located at the beginning of the common iliac, which was ligated. Eventual subsidence of the generalized and local infection took place.

Extension of thrombophlebitis from the saphenous to the deep system is not rare. If the process in the internal saphenous vein extends into the groin, a venogram will be useful as a guide to therapy. We, like Welch and Faxon[10], have found deep phlebitis of the lower leg by venography when a superficial phlebitis in the external saphenous system obscured the local evidence in the calf muscles. Division of the deep as well as the superficial veins is advisable in this situation.

SUMMARY AND CONCLUSIONS

Further experience, based on a policy of division of the femoral vein for the prevention of embolism in *all* cases of thrombophlebitis of the deep veins in the lower leg, has led us to the following conclusions:

1. Division of the common femoral vein will cause early resolution of the thrombophlebitic process in the lower leg. Edema of the lower leg appears not to be aggravated; indeed the process frequently disappears more rapidly than might be expected. In occasional instances edema increases after vein division, but we are not aware of a valid reason for attributing the result to vein division.

2. Our former practice of dividing the femoral vein, by preference below the entrance of the vena profunda, has been abandoned in favor of division above, because of an occasional instance of embolism from the vena profunda.

3. When thrombophlebitis of the lower leg is present, division of the common femoral vein is preferable to heparinization or paravertebral novocain block *as a prophylactic measure against embolism.* We do not wish to imply that vein division is superior to these measures for the treatment of the local process *per se.*

4. There are occasional individuals in whom the process does not remain confined to the deep veins in the lower leg. A new focus of thrombosis above the site of vein division may develop and embolism may then occur. In this event the patient must be reclassified as one with iliofemoral thrombophlebitis and treated accordingly.

5. The treatment of iliofemoral thrombophlebitis by clot or thrombus extraction *via* the common femoral or iliac veins, followed by division of either of these veins is a valuable and at times indispensable procedure, but we do not feel that it need be adopted as a routine measure. Heparinization or paravertebral novocain block may be as satisfactory or even superior for the purpose of securing symptomatic relief. However, if one infarct should occur, regardless of what type of management has been in effect, it is our view that division of either the common femoral or iliac vein above the site of, or after extraction of, the clot or thrombus should be performed.

6. Venography is an indispensable technic for the correct management of all types of thrombophlebitis of the lower extremity. A filling defect in the venogram does not prove the presence of thrombophlebitis unless the element of vasospasm can be ruled out. Until an effective method for achieving this during venography becomes available the venogram should be interpreted in the light of the concomitant clinical picture.

7. The varying circumstances in which venography can be useful are described.

BIBLIOGRAPHY

[1] Fine, J., and Sears, J. B.: The Prophylaxis of Pulmonary Embolism by Division of Femoral Vein. ANNALS OF SURGERY, **114,** 801, 1941.

[2] Barker, N. W., Nygaard, K. K., Walters, W., and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism. Proc. Staff Meet., Mayo Clinic, **15,** 769, 1940; **16,** 1, 17, 34, 1941.

[3] Pilcher, R.: Postoperative Thrombosis and Embolism. Lancet, **2**, 628, 1939.
[4] Frykholm, R.: Pathogenesis and Mechanical Prophylaxis of Venous Thrombosis. Surg., Gynec., and Obst., **71**, 307, 1940.
[5] Neuman, R.: Centers of Origin and Forms of Development of Thrombosis of the Leg. Arch. f. path. Anat., **301**, 708, 1938.
[6] Roesslé, R.: On the Significance and Origin of Venous Thrombosis of the Lower Legs. Arch. f. path. Anat., **300**, 180, 1937.
[7] Hunter, W. C., Sneeden, V. D., Robertson, T. O., and Snyder, G. A. C.: Thrombosis of the Deep Veins of the Leg. Arch. Int. Med., **68**, 1, 1941.
[8] Belt, T. H.: Thrombosis and Pulmonary Embolism. Am. J. Path., **10**, 129, 1934.
[9] Homans, J.: Thrombosis of Deep Veins of Lower Leg Causing Pulmonary Embolism. N. E. Jour. Med., **211**, 993, 34. Venous Thrombosis in Lower Limbs. Am. Jour. Surg., **38**, 316, 317. Circulatory Diseases of Extremities. Macmillan, 1939. Exploration and Division of the Femoral and Iliac Veins in the Treatment of Thrombophlebitis of the Leg. N. E. Jour. Med., **224**, 179, 1941.
[10] Welch, Claude E., and Faxon, Henry H.: Thrombophlebitis and Pulmonary Embolism. J. A. M. A., **117**, 1502, 1941.
[11] Sears, J. B.: Experience with Femoral Vein Ligation for Prophylaxis of Postoperative Pulmonary Embolism. N. E. Jour. Med., **224**, 108, 1941.
[12] Ochsner, A., and DeBakey, M.: Therapy of Phlebothrombosis and Thrombophlebitis. Arch. Surg., **40**, 208, 1940.
[13] Bauer, G.: Venographic Studies of Thrombo-Embolic Disease. Acta Skand. Chir., Supplement 61, 1940.
[14] Hampton, A. O., and Castleman, B.: Correlation of Postmortem Chest Teleroentgenograms with Autopsy Findings. Am. Jour. Roentgenol., **43**, 305, 1940.
[15] Johnson, A. S.: Antemortem Recognition of Pulmonary Embolism. N. E. Jour. Med., **222**, 793, 1940.
[16] Barnes, A. R.: Pulmonary Embolism. J. A. M. A., **109**, 1347, 1937.
[17] Ochsner. A., and DeBakey, M.: Therapeutic Considerations of Thrombophlebitis in Phlebothrombosis. N. E. Jour. Med., **225**, 207, 1941.
[18] McCartney, J. S.: Quoted by Barnes, A. R.[16]
[19] Collins, D. C.: Pulmonary Embolism: Based upon a Study of 271 Instances. Am. J. Surg., **33**, 210, 1936.
[20] Barker, N. W.: Primary Idiopathic Thrombophlebitis. Arch. Int. Med., **58**, 147, 1936.
[21] Culp, O. S.: Postoperative Venous Thrombosis and Pulmonary Embolism: Analysis of 88 Cases. Bull. Johns Hopkins Hosp., **67**, 1, 1940.
[22] Läwen, A.: Further Experiences with Thrombectomy in Venous Thrombosis. Arch. Klin. Chir., **193**, 723, 1938.
[23] Kulenkampff, D.: The Prevention of Severe and Fatal Emboli by Evacuation of the Iliac Vein. Arch. Klin. Chir., **193**, 727, 1938.
[24] Linde, S.: On the Incidence of Thrombo-Embolism Following Surgical Operation, and its Influence on the Length of the Recumbent Period. Acta Medica Scand., **107**, 165, 1941.
[25] de Takats, G., and Jesser, J. H.: Pulmonary Embolism. J. A. M. A., **114**, 1415, 1940.

DISCUSSION.—DR. HERMAN E. PEARSE (Rochester, N. Y.): Dr. Fine has given a very excellent discussion of the treatment of this condition, and I would like to add one word on its prevention. Welch showed that one essential factor in the propagation of intravascular clotting was stasis. The postoperative period is one of stasis in the veins of the lower extremities. I believe that much of this intravascular clotting can be prevented by adequate leg exercises in the immediate postoperative period.

DR. ALTON OCHSNER (New Orleans, La.): I am sure we are all deeply indebted to Dr. Fine for this presentation relative to thrombophlebitis. In our experience, we believe one must differentiate between two types of clotting, namely, those in which there is

inflammatory disease: and those in which there is no inflammation, which we have designated as phlebothrombitis. In both of these there are the same factors responsible, i. e., the changes in blood constituents which are the result of tissue damage. These may be the result of trauma: the result of invasion by infection: or neoplastic disease.

In the patient with thrombophlebitis, we feel, with few exceptions, unless suppuration has occurred ligation of the vein is not necessary, because in these instances the clot is firmly attached and there is no danger of it becoming detached. If one will treat these patients by wrapping the extremity, and preventing propagation of the thrombus above the area of thrombophlebitis, there is little danger of detachment of the clot. These we feel are best treated by novocain block of regional sympathetic ganglia. We have had prompt subsidence of symptoms.

There are a few cases of thrombophlebitis, and this is particularly associated with pelvic thrombophlebitis, in which ligation of the vein is necessary. These are infected emboli. Recently Dr. Conrad Collins, of the Department of Gynecology, has tied off eight vena caval successfully in patients who had puerperal infections, with infected emboli breaking off.

In the patient who has a phlebothrombosis, there is little evidence of disease. It is this patient who gets up out of bed after operative procedure and develops embolism. We can detect these by suspecting, and I know no condition in which suspicion is more valuable. It has become a rule in our clinic that any patient past forty years of age, who has an operative procedure, or who has an inflammatory process, or neoplastic disease, has careful routine examination of his lower extremities. We measure the extremities, and not only perform the Homan's test, which is the dorsal flexion of the foot, but carefully examine the plantar aspects of their feet, because this is one of the areas in which the thrombi may originate. In these individuals, if there is some tenderness, phlebography must be done, and, if the phlebogram shows a defect, then the vein should be tied off. We not only tie off the vein but we suck out the clot proximal to the wound, which I am sure Dr. Fine does, too.

It is of importance, I think, to realize that heparin will not necessarily protect these cases. I have recently seen a patient who had five emboli, four of which occurred in 21 days, during which time he received heparin continuously. His clotting time ranged from 15 minutes to one-half hour. It was only after his fifth one that a phlebogram was made, and his vein was tied off, which prevented a fatal outcome.

If one will recall that 71 per cent of the patients who have fatal pulmonary emboli have had an antecedent infarction, it certainly is an indication to us that any patient who has infarction should at least be given advantage of a phlebogram. By means of phlebography, with the exceptions which Dr. Fine has brought out, namely, spasm, and possibly some cases in which there is absence of filling, one can determine quite accurately whether there is a clot or not, and the ligation of the vein in such an instance is certainly life-saving.

DR. LELAND S. MCKITTRICK (Boston, Mass.): I would like to say just a word in support of what Dr. Fine has talked to you about. We, in the Peripheral Vascular Clinic, at the Massachusetts General Hospital, have been much interested in this group of patients. We are not able—and I say this with apologies—to draw this clear-cut distinction that Dr. Ochsner has just spoken to you about, between the two groups that he has so ably described. Heparin has let us down, or possibly we have let heparin down. In any case, we have not received from heparin the same satisfactory results that the group in Toronto has.

In our Peripheral Vascular Clinic we have a group which, I think, speaks quite independently. Sometimes we agree and frequently we disagree. The group is in complete agreement upon the value and importance of an attack upon the venous tree in cases of thrombophlebitis or phlebothrombitis (I am including them all together). We also are in complete agreement upon the safety of the method. We are in agreement upon the difficulty of interpreting the venograms, particularly those of the veins below the level of the popliteal.

We are in complete disagreement as to the technic of obtaining venograms. We are in disagreement as to their importance, because of the doubt in the minds of many of us at the present time as to whether we can interpret venograms with sufficient accuracy to give them more significance than a very careful clinical examination of the part. We are in disagreement as to the level at which the vein should be opened and ligated.

I say "opened and ligated" because the vein should never be constricted until it is first

opened to exclude the presence of a thrombus at the level at which the ligature is to be applied.

So I leave it at that point. We believe in the procedure, at least in the principles of it, but the many, many things about which we are not in agreement make this a particularly lively and interesting subject at the present time.

DR. JACOB FINE (closing): With reference to Dr. Ochsner's distinction between thrombophlebitis and phlebothrombosis, I think the detailed text of this paper will show that from the point of view of embolism this distinction is not helpful clinically, for we have seen embolism in individuals with outspoken thrombophlebitis.

Dr. Pearse's reference to leg exercises to minimize the occurrence of venous thrombosis is well taken. We adopted that principle in our clinic years ago, and I think it is a well known principle, but unfortunately we continue to get thrombosis in spite of the use of leg exercises.

As to ligation *versus* division of the vein, we are in complete agreement with what Dr. McKittrick says. We always divide the vein, but we always open it before dividing it, and if there is a clot at the site of the femoral vein it is removed. If it cannot be removed, we consider it desirable to divide the iliac vein if embolism has occurred or if it occurs subsequently.

ANNOUNCEMENT OF FELLOWSHIPS IN MEDICINE AND PUBLIC HEALTH

THE COMMONWEALTH FUND of New York, a philanthropic foundation established in 1918 by the late Mrs. Stephen V. Harkness, announces that it is offering through the Pan American Sanitary Bureau fifteen fellowships for one year's study of public health subjects or postgraduate medical courses to properly qualified persons who are citizens of the other American republics. Fellowships in public health will be open to physicians, sanitary officers, technicians, public health nurses, etc. These fellows will be selected through a system of cooperation with medical and health authorities of the different countries concerned, and whenever deemed advisable they will be interviewed by traveling representatives of the Pan American Sanitary Bureau. Each fellowship will provide living allowances while the holder is in the United States, travel costs, and tuition. Knowledge of the English language will be among the requirements, and also the possession of certain specific qualifications.

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THE CONTROL OF HAIR AND FEATHER PIGMENTATION AS REVEALED BY GRAFTING MELANOPHORES IN THE EMBRYO*

B. H. Willier, Ph.D., D.Sc.

Baltimore, Md.

FROM THE DEPARTMENT OF BIOLOGY, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.

This talk deals with the mechanism of pigmentation in hairs and feathers, one of the major problems in animal biology. You are already familiar with variations in the color of human hair, also with the fact that many animals show regional differences in the color of the hair or feather —as, for example, the spotted patterns of the Dalmatian dog, the leopard, Holstein cow or the guinea fowl and with the striped patterns of the zebra, tiger and the Barred Plymouth Rock feathers. It is not my intention this morning to present an explanation of how these color patterns are produced, but merely to give you a glimpse into the nature of the problem involved in their formation.

Specifically, we shall examine (1) the source of the pigment cells in the embryo; and (2) the mode of formation of pigment in hair and especially in feathers which have been studied much more extensively.

Method.—The method which we use in our experimentation is to graft small bits of tissue (usually less than one millimeter in greatest dimension) from one embryo, the donor, into another embryo, the host. The host chick embryo is prepared for receiving the graft by first sawing a window by means of a hacksaw in the shell directly over the embryo, whose exact position is located by candling. The shell window is removed, and the shell membrane is slit open so as to expose the body of the embryo. The embryo is now viewed through a binocular dissecting microscope and a small incision is made in the body wall for receiving the graft tissue. Next, the piece of tissue which has been isolated from the donor embryo by means of fine steel dissecting needles is transferred to the host embryo and pushed into the graft incision. The shell window is then returned to its position and sealed in by means of melted paraffin, and the egg returned to the incubator.

The Source of Pigment Cells.—From several lines of evidence (for a detailed consideration see Rawles, 1940, Ris, 1941, Willier, 1941, and Willier and Rawles, 1940) it has been proved that the precursor pigment cells arise in the neural crest and migrate into the skin and its derivatives, the hair and feather follicles. Two main types of experiments will be presented here. The wing-bud is excised from an embryo of a pigmented breed of fowl, the Barred Plymouth Rock, and grafted into the coelom of a White Leghorn host chick embryo. A wing-bud from an 85-hour embryo grown in the coelom of the host embryo develops into a normal-appearing wing covered

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with black down feathers, as you would expect since it came from a Barred Rock donor. If, however, the same experiment is done using a wing-bud from a donor embryo of 70-hours incubation the result is quite different. A normal wing forms but is covered with skin having white down feathers. These results show that the pigment cells arise outside of the wing-bud and migrate into it between 70 and 85 hours of incubation.

My research assistant, Dr. Mary E. Rawles (1940), has carried out similar experiments with the mouse embryo. A strain of genetically black mice was used. The mouse embryo at about 11 days of gestation is removed from the uterus and pieces of skin ectoderm are isolated from two regions of the embryo, one over the neural crest and one from the forelimb-bud. If the skin ectoderm contains neural crest cells it will produce, when transplanted to the coelom of a White Leghorn host embryo, typical skin and hair follicles, including pigment cells. If, on the other hand, a piece is taken from the limb-bud of the same embryo the result is the same except that there are no pigment cells whatsoever present in the hair follicles. By means of these two types of analysis along with certain other experimental evidence (Ris, 1941), we have been able to prove conclusively that the pigment cells are derived solely from the neural crest. Moreover, the results show that the neural crest cells migrate laterally and invade the skin, the hair and feather follicles and furnish melanin pigment to these structures. In the absence of neural crest cells the hair and feather develop normally but without any pigment.

Grafting of Precursor Pigment Cells.—In this type of experiment neural crest cells (potential melanophores) are grafted from one embryo to another of equivalent ages, i.e., about 70-hours incubation. The donor and host embryos are of different breeds of fowl or species of bird. Neural crest cells from the donor are transplanted to the base of the wing-bud of the host before its own neural crest cells have migrated into the wing-bud. This results in the formation of an area of donor-colored down feathers on the wing and adjacent regions of the body in a majority of cases. The down plumage is replaced by juvenile contour feathers having the shape, rate of growth and distribution in tracts characteristic of host control chicks, but invariably having the color or color pattern of the donor breed or species. This was found to be true for all donor breeds and species tested such as Barred Plymouth Rock, New Hampshire Red, Black Minorca, Brown Leghorn, White Wyandotte, White Silkie and White Plymouth Rock, crow, robin, ring-neck pheasant. The results are interpreted to mean that grafted melanophores enter the wing before the host ones do and take up all the available positions in the skin and feather follicles. The host melanophores migrate later into the wing from their seat of origin in the neural crest. Since, however, they have entered later than the donor melanophores, they remain outside of the feather follicles in the dermis of the skin.

Cooperation of Donor Melanophores and Host Feather Follicle.—It is thus clear that two component parts differing in their genetic constitution

cooperate in the production of the donor colored feathers in the host. The feather follicle is the embryonic organ which builds the structural elements of the feather. The melanophore furnished by the donor, on the other hand, is the pigment producer. The melanophore is a branched cell containing melanin pigment granules. When introduced into the host embryo the melano-

FIG. 1.—A 29-day-old White Leghorn male chick showing barred plumage on the right wing and breast. Produced by grafting potential melanophores from an 18-hour-old Barred Plymouth Rock embryo into the base of the wing-bud of the host embryo at 79-hours incubation.

FIG. 2.—A 22-day-old Barred Plymouth Rock chick showing white plumage on the right wing. Produced by grafting neural crest cells (potential melanophores) from a 71-hour-old White Silkie Bantam embryo into the base of the wing-bud of the host embryo at 70-hours incubation.

phores from pigmented breeds of fowl migrate into the developing feather follicle and take up positions next to the epidermal cells forming the parts of the feather. The melanophore sends out several processes which come in close approximation to the epidermal cells. The tips of the processes extrude pigment granules which are taken into the host epidermal cells. The granules which the host epidermal cells thus acquire are donor specific as to size, shape, and color. When melanophores from the white breeds of fowl are grafted to pigmented breeds, they migrate into the host feather follicles just as melanophores from pigmented breeds do, but die before depositing any pigment granules, hence a white host feather is produced. Apparently the melanophore of the white breeds possess a lethal factor which brings about its early death.

The question now arises as to how donor melanophore and host feather follicle work together in the production of a specific coloration or color pattern. That the donor melanophores react to extrinsic factors in the host feather follicles is illustrated by the striking variations in color pattern produced in the various feathers of the same bird. Barred Rock melanophores in a White Leghorn host produce color patterns, ranging from those almost wholly black to those with distinct black and white bars. Measurements of the increase in length of the growing feather show that if the growth rate is rapid (certain flight feathers) the feather tends to be all black except for traces of white bars on the shaft and when slow (breast feather) the black and white bars are distinct and nearly equal in width. Generally speaking, rapid growth rate favors a greater deposition of black pigment than a slow rate.

Similar variations in color pattern have been produced by guinea fowl melanophores in White Leghorn host feathers. In rapidly growing feathers the vane is gray with tan-brown tips and the outer vane margins are mottled brownish-gray. In slowly growing ones the feather shows cream-white bars on a gray background. Thus another example is furnished showing that the color pattern formed varies with the rate of growth and position of the feather on the host. It ranges from a mottled pattern to one which is typically barred.

Summarizing then, it is evident that the individual feather follicle alters greatly the type of pattern produced by the donor melanophores. Each feather follicle produces its own specific type of pattern.

Rôle of Hormones in Feather Pigmentation.—That endocrine substances have an affect on melanophores is brought out in various ways. Lillie and his associates (Lillie, 1932) have shown that thyroxin injected into Brown Leghorn males affect profoundly the pigmentation pattern produced in a regenerating neck hackle feather. The thyroxin produced an extension of the black pigment. By controlling the dosage and time of introduction interesting atypical pigmentation patterns can be produced in the feather.

Also, these investigators have shown that sex hormones may also modify feather color patterns in the Brown Leghorn fowl. In this fowl the breast

feather is black in the normal male and capon and salmon-colored in the normal female. If a breast feather of a capon is plucked and the female sex hormone estrone is injected at suitable times during its regeneration, a salmon-colored bar is formed across the feather vane. Thus a female colored bar is produced on a male colored background. Similarly, male colored bars may be produced in regenerating breast feathers by omitting every seventh day an otherwise daily injection of female sex hormone. In these experiments we have evidence that the female hormone favors the differentiation of a type of melanophore which deposits salmon-colored pigment.

Recently Hamilton (1941), working in my laboratory, has studied the action of the sex hormones and desoxycorticosterone on the differentiation of melanophores cultivated in plasma clots *in vitro*. He found that skin ectoderm explants of the N. H. Red embryo both estrone and testosterone propionate bring about the differentiation of red melanophores (typically only infrequently present in control cultures). Also the adrenal hormone, desoxycorticosterone, has an inhibitory action on the differentiation of Barred Rock melanophores. If a piece of skin ectoderm from a seven-day embryo of this breed is cultivated in a plasma clot containing 100 *gamma* of this substance per cubic centimeter no melanophores differentiate. If the clot contains 67 *gamma* per cubic centimeter many degenerate melanophores are found along with a few expanded ones.

These experiments show that melanophores have the capacity to respond to hormones and thus furnish a basis for understanding the rôle of hormones in feather pigmentation.

SUMMARY

1. Melanophores arise from the neural crest and migrate into the skin and its derivatives, the hair and feather follicles.

2. Hair and feather follicles build the hair and feather, respectively. In the absence of melanophores both hair and feather are white but normal structurally.

3. Melanophores from pigmented breeds of fowl deposit specific melanin pigment granules into the epidermal cells of the host feather. Melanophores from white breeds penetrate the feather follicles of potentially pigmented hosts but deposite no pigment granules. These are lethal cells which die before they have time to deposit pigment granules. A genetic lethal factor in the melanophore is postulated as causing gray hair in man.

4. By grafting melanophores from one breed of chick embryo to another it is possible to show the respective rôles of the melanophore and feather follicle in the formation of pigmentation patterns. The specific color or pattern produced depends upon the genetic constitution of the melanophore and partly upon the physiology of the feather follicle, i.e., its growth rate, reaction threshold, etc. They work together in forming a specific color pattern.

5. Hormones modify greatly the direction of differentiation and action

of melanophores. They have a profound effect on the melanophores during the process of color pattern formation in a developing feather.

REFERENCES

Hamilton, H. L.: Influence of Adrenal and Sex Hormones on the Differentiation of Melanophores in the Chick. Jour. Exp. Zool., **88,** 275–305, 1941.

Lillie, F. R.: The Physiology of Feather Pattern. Wilson Bulletin, **44,** 193–211, 1932.

Rawles, Mary E.: The Development of Melanophores from Embryonic Mouse Tissues Grown in the Coelom of Chick Embryos. Proc. Nat. Acad. Sci., **26,** 673–680, 1940.

Ris, Hans.: An Experimental Study on the Origin of Melanophores in Birds. Physiol. Zool., **14,** 48–66, 1941

Willier, B. H.: An Analysis of Feather Color Pattern Produced by Grafting Melanophores during Embryonic Development. Amer. Nat., **75,** 136–146, 1941.

Willier, B. H., and Rawles, Mary E.: The Control of Feather Color Pattern by Melanophores Grafted from One Embryo to Another of a Different Breed of Fowl. Physiol. Zool., **13,** 177–199, 1940.

AN EXPERIMENTAL APPROACH TO THE PROBLEM OF MENSTRUAL DISORDERS*

JOHN C. BURCH, M.D.,

AND

DORIS PHELPS, PH.D.

NASHVILLE, TENN.

FROM THE DEPARTMENT OF OBSTETRICS AND GYNECOLOGY, VANDERBILT UNIVERSITY SCHOOL OF MEDICINE, NASHVILLE, TENN.

FOR THE PAST 13 YEARS our little group has been engaged in an experimental study of the disorders of menstruation. Our purpose is to discuss, briefly, the experimental approach to this problem, to describe some of our current experiments, and to relate these to past work and to the problem as a whole.

Primarily, the phenomenon of menstruation is an expression of endocrine activity; by means of ovarian hormones, the endometrium is stimulated. Later, as a result of certain changes in the concentration of the hormones, the endometrium undergoes a phase of regression which is characterized by the appearance of menstruation. The problem of abnormal menstruation can, therefore, be said to have a central phase dealing with various lesions of the endocrine system, a hormonal phase which deals with the ebb and flow of the ovarian hormones and a peripheral phase dealing with the vascular changes in the end-organ or endometrium.

For descriptive purposes it is best to begin with the changes in hormone concentration which are responsible for the initiation of menstruation. Many observers had noted the premature appearance of menstruation following the removal of a corpus luteum or oophorectomy. Allen[1] observed a similar premature menstruation in monkeys subjected to castration and also noted the premature appearance of menstruation following surgery to large graafian follicles. In further experiments, Allen injected castrated monkeys with estrogen in oil for nine to 20 days. Three to ten days after the cessation of estrogen injections, menstruation appeared. Many investigators have confirmed this observation of uterine bleeding in castrated individuals following the cessation of treatment with estrogen. Such estrogen-withdrawal bleeding can be indefinitely postponed by following the estrogen treatment with progesterone, but when the progesterone is discontinued, bleeding occurs. Bleeding does not occur during treatment with ovarian hormones as long as the amount of hormone available remains above a certain so-called critical level. It may occur during treatment with estrogen if the daily dose is suddenly reduced below this level, or if estrogen withdrawal is followed by treatment with small daily doses of progesterone. If both hormones have been administered, bleeding occurs following progesterone withdrawal, even when estro-

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gen is continued in amounts which would have been sufficient to prevent bleeding had no progesterone been given. If, in these circumstances, very large amounts of estrogen are given following progesterone withdrawal, bleeding may not occur until after the estrogen injections are discontinued.

These facts, and many others of similar import, have led to the conclusion that a decline in the level of ovarian activity is an essential prerequisite for the onset of menstruation.

The vascular phenomena characteristic of normal menstruation in the rhesus monkey have been described by Markee,[2] who observed the process in bits of endometrium transplanted to the anterior chamber of the eye. Decrease in the size of the intra-ocular transplants always precedes and accompanies menstrual bleeding. When the area of the transplant has decreased 20 to 30 per cent, the circulation in the superficial part of the endometrium becomes slower and slower until a condition of stasis or near stasis exists. Four to 24 hours before bleeding begins, the coiled arteries which supply the upper one-half to two-thirds of the endometrium constrict, rendering the whole transplant ischemic. Vasoconstriction persists throughout the menstrual period. However, following the initial period of ischemia, individual arteries relax temporarily, a few at a time, and when this happens, hemorrhage occurs. Most commonly, blood escapes through a break in the wall of an arteriole or capillary and forms a hematoma which subsequently ruptures. It may break through the uterine epithelium without forming a hematoma. Also, diapedesis with or without hematoma formation may occur and a venous flow may take place in fields of previous hemorrhage and destruction of tissue. Reestablishment of the circulation terminates menstruation.

The experimental bleeding which results from the types of hormone treatment previously described is similar to normal menstruation as regards amount, duration and local vascular phenomena. In spite of a vast amount of investigation relating to menstruation in general, little or nothing has been learned concerning the local mechanisms involved in the production of menstrual abnormalities. In 1941, our colleague, Dr. Rucker Cleveland,[3] then of the Department of Anatomy, noted the occurrence of prolonged bleeding in castrated monkeys which had received estrogen and progesterone simultaneously, following an initial 14-day period of treatment with estrogen alone. As far as we have been able to find, this is the first reported instance of an experimentally produced menorrhagia. Doctor Cleveland's observation suggested a study of the vascular changes in the endometrium during this type of prolonged bleeding. Accordingly, intra-ocular endometrial transplants were made in four castrated monkeys. These animals were then injected with estrogen and progesterone, as in Doctor Cleveland's experiments. Vaginal bleeding of 15 to 23 days' duration followed cessation of treatment. During the first three to five days there was a profuse flow of red blood; subsequently, the flow was less profuse and the color was red at times but, on the whole, darker. The changes observed in the transplants were essentially similar to those described by Markee.[2] Hemorrhage was observed

only during the first day or so of vaginal bleeding; subsequently, the transplants remained anemic until shortly before or after the cessation of vaginal bleeding. At this time, restoration of the circulation and some regeneration of tissue were noted. These observations suggest that the initial breakdown of the tissue proceeded more or less on schedule and that the prolongation of bleeding was due primarily to delayed restoration of the circulation.*

This method of study, while it promises to give some insight into the mechanism of menorrhagia, does not afford any information concerning the central phase of the problem of menstrual disorders, nor concerning the changes in endometrial histology which are associated with abnormal bleeding. We have approached these phases of the problem from another angle, and the results of our studies have yielded information concerning the endocrine changes ultimately responsible for abnormalities of menstruation. The conclusions are of importance and rest upon the following experimental basis.

Our earlier experiments[4] were undertaken in an attempt to obtain evidence concerning the etiology of glandular cystic hyperplasia of the endometrium. Castrated mice were injected with small daily doses of estrin and progestin, singly and in combination. Their endometria were compared with human endometria, from the various phases of the cycle and with specimens of glandular cystic hyperplasia. The endometrial reactions of the estrin-treated mice and of the human endometria from the first 14 days of the cycle were identical, and, except for a lesser degree of proliferation and the absence of cystic glands, were similar to glandular cystic hyperplasia. This suggested that an increased estrogenic stimulus might produce hyperplasia. Accordingly, castrated guinea-pigs were injected with larger doses for a longer period of time. Typical glandular cystic hyperplasia resulted.[5] In these animals, the vaginal smears showed a continuous estrous reaction. Just about this time, Haterius,[6] and Emery,[7] reported the occurrence of continuous estrus following extreme partial castration. The application of this procedure to the study of hyperplasia was obvious.

Meanwhile, we, and many others as well, were engaged in an attempt to correlate the disturbances of menstruation with endometrial changes. The endometrial biopsy technic which we introduced about this time[8, 9] was of great help in the collection of the necessary data, which showed, conclusively, that any kind of a menstrual disturbance could arise from any kind of endometrium. Due to the fact that such opposite symptoms as amenorrhea and menorrhagia could both arise from the same type of endometrium, many competent observers referred different symptoms to different glands, and such terms as thyroid menorrhagia and pituitary amenorrhea were common. Some even thought that the association of a particular glandular lesion with a particular symptom was of primary diagnostic import. The results of our partial castration experiments[10] shed considerable light on these points. Guinea-

* These experiments were supported by a grant from the S. E. Massengill Co. The hormones used (Progynon-B and Proluton) were kindly supplied by the Schering Corporation, through the courtesy of Drs. Erwin Schwenk and Bradley Whitman.

pigs were partially castrated and observed for 110 days. In some animals the estrous cycle continued normally; in a second group, there was continuous estrus and in another group estrus occurred infrequently or not at all. In the animals with normal cycles the ovaries showed small and infrequent corpora lutea and the endometria showed a fairly normal estrogenic stimulus but a deficient progesterone stimulus. In the group with long periods of estrus the ovaries were cystic and contained no corpora lutea. The endometria showed characteristic glandular cystic hyperplasia. In the animals with no cycles or infrequent estrus, the ovarian fragments were small and contained no corpora lutea and the endometria showed a deficient estrogenic stimulus and lack of any progesterone stimulus.

Thus, with experimental ovarian failure three different groups of individuals could be distinguished by changes in the sex cycles and endometria.

Studies of human endometria revealed that women with menstrual disorders could be classified in three similar groups, characterized, respectively, by (1) evidence of a deficient progesterone stimulus in the endometrium, corpus luteum in the ovary; (2) marked proliferation in the endometrium, no corpora lutea in the ovaries; and (3) minimal or no proliferation in the endometrium, ovaries atrophic. While there was no absolute correlation between the type of endometrial reaction and the type of menstrual disorder, there was a tendency for the milder types of menstrual disorders to be associated with endometrial reactions of the first type, excessive bleeding with those of the second type and amenorrhea with those of the third type. These observations led to the important conclusion that the various endometrial changes in these cases result from different degrees of ovarian failure. In general, three levels of ovarian failure can be distinguished. In the interest of simplicity we have designated them as the first, second and third degrees of ovarian failure. These are not static or sharply delimited conditions. Each merges gradually into the next and within each category there are variations in the level of ovarian activity.

With this picture of ovarian failure established, it was only natural to attempt the production of a similar picture by other means which would reduce the function of the ovary. Since hypophysectomy completely abolishes ovarian function it seemed logical to expect that partial hypophysectomy would produce a partial ovarian failure. Therefore, a number of guinea-pigs were partially hypophysectomized and observed for 110 days. These animals showed changes in the sex cycle and endometrium identical with those observed in the partial castration experiments.[10]

Under normal conditions sexual periodicity is dependent upon the proper adjustment of the hypophyseal-ovarian relationship. The above experimental results illustrate the fact that similar abnormalities in the genital tract can be produced by altering either component of the relationship. Clinical evidence indicates that a variety of other conditions, such as lesions of other glands or constitutional conditions or nutritional deficiencies, can alter the hypophyseal-ovarian relationship and produce changes in the genitalia. We

have some experimental evidence confirmatory of this supposition. In thyroidectomized animals the picture of ovarian failure is identical with that seen in the animals subjected to partial castration or partial hypophysectomy.[11] A somewhat similar picture has recently been observed in animals afflicted with a general constitutional disease, chronic cecitis. In animals with experimental hypertension resulting from partial nephrectomy, there was definite evidence of lowered ovarian function.[12]

Many investigators have obtained experimental evidence confirmatory of that described above. The production of glandular cystic hyperplasia by prolonged treatment with estrogen has been demonstrated in all of the common laboratory animals.[13–17] Production of the typical endometrial picture in the macaque by this means has recently been reported from our own laboratory.[18] The results of our partial castration experiments have been confirmed repeatedly.[19, 20] The interesting experiments of Ranson, and his collaborators,[21] on the effects of hypothalamic lesions are highly suggestive as to the mechanism of pituitary dysfunction. Abundant clinical evidence is also at hand which parallels the conclusions drawn from our experimental data. From all of the evidence, we have formulated the following general concept of menstrual disorders. To state it briefly:

Functional menstrual disorders result from an ovarian failure. This may be primary, due to inherent ovarian disease, or secondary, due to extra-ovarian causes, such as pituitary, thyroid or other endocrine disease and various types of constitutional disease. The approximate degree of ovarian involvement is indicated by the endometrium. There is no constant correlation between the primary lesion, the menstrual symptom and the endometrial reaction.

REFERENCES

[1] Allen, E.: The Menstrual Cycle of the Monkey, Macacus Rhesus: Observations on Normal Animals: The Effects of Removal of the Ovaries and the Effects of Injections of Ovarian and Placental Extracts into the Spayed Animals. Contrib. Embryol. (No. 98), Carnegie Inst. Washington, **19**, 1, 1927.

[2] Markee, J. E.: Menstruation in Intra-ocular Endometrial Transplants in the Rhesus Monkey. Contrib. Embryol. (No. 177), Carnegie Inst. Washington, **28**, 221, 1940.

[3] Cleveland, R.: Observations on Hormone-Withdrawal Bleeding in Castrated Macaques. Endocrinol., **29**, 343, 1941.

[4] Burch, John C., Williams, W. L., and Cunningham, R. S.: The Etiology of Endometrial Hyperplasia. Surg., Gynec., and Obstet., **53**, 338, 1931.

[5] Burch, John C., Wolfe, J. M., and Cunningham, R. S.: Experiments on Endometrial Hyperplasia. Endocrinol., **16**, 541, 1932.

[6] Haterius, H. O.: Vaginal Cornification and Ovarian Blood Supply. Anat. Rec., **47**, 318, 1930.

[7] Emery, F. E.: Changes in the Ovary and the Estrous Cycle Following the Removal of One Ovary in Albino Rats. Physiol. Zool., **4**, 101, 1931.

[8] Burch, John C., and Klingler, H. H.: Endometrial Biopsy by Suction. Jour. Tennessee State Med. Assn., **25**, 142, 1932.

[9] Klingler, H. H., and Burch, John C.: Suction in Obtaining Endometrial Biopsies. J.A.M.A., **99**, 559, 1932.

[10] Burch, John C., McClellan, G. S., Johnson, C. D., and Ellison, E. T.: The Diagnosis and Classification of Menstrual Disorders. J.A.M.A., **108**, 96, 1937.

[11] Williams, C., Phelps, Doris, and Burch, John C.: Observations on the Effect of Hypothyroidism on Ovarian Function in the Guinea-pig. Endocrinol., **29**, 373, 1941.

[12] Diaz, J. T.: Effect of Subtotal Nephrectomy upon Estrous Cycle of the Albino Rat. Proc. Soc. Exper. Biol. and Med., **45**, 226, 1940.

[13] Parkes, A. S.: Experimental Endometrial Hyperplasia. Lancet, **1**, 485, 1935.

[14] Tietze, K.: Die Follikelpersistenz mit glandulärer Hyperplasie des Endometriums in vergleichend pathologischer, experimenteller und genetischer Beziehung. Ztschr. f. Geburtsh. u. Gynäk., **108**, 79, 1934.

[15] Zuckerman, S., and Morse, A. H.: The Experimental Production of Excessive Endometrial Hyperplasia. Surg., Gynec., and Obstet., **61**, 15, 1935.

[16] Zuckerman, S.: Cystic Endometrial Hyperplasia in the Rhesus Monkey. Jour. Obstet and Gynæc. Brit. Emp., **44**, 494, 1937.

[17] Nelson, W. O.: Endometrial and Myometrial Changes, Including Fibromyomatous Nodules, Induced in the Uterus of the Guinea-pig by the Prolonged Administration of Oestrogenic Hormones. Anat. Rec., **68**, 99, 1937.

[18] Cleveland, R., Phelps, D., and Burch, John C.: The Experimental Production of Glandular Cystic Hyperplasia in Castrated Macaques. Endocrinol., **28**, 659, 1941.

[19] Lipschütz, A.: Hyperplasia experimentale de l'endomètre avec prolifération atypique de l'épithélium utérin après des interventions ovariennes. Gynéc. et obset., **36**, 408, 481, 1937; and **37**, 17, 1938.

[20] Schmidt, I. G.: Changes in the Genital Tracts of Guinea-pigs Associated with Cystic and "Interstitial Gland" Ovaries of Long Duration. Endocrinol., **24**, 69, 1939.

[21] Dey, F. L.: Changes in Ovaries and Uteri in Guinea-pigs with Hypothalamic Lesions. Am. Jour. Anat., **69**, 61, 1941.

DISCUSSION.—DR. JOE VINCENT MEIGS (Boston): Doctor Burch has clearly described his interesting work and his interpretation of it. There is no doubt that menstruation is a circulatory phenomenon, partially, but not wholly, controlled by ovarian hormones. There is no doubt that the ovary, if normal, controls the normal endometrium of a normal uterus, but menstruation or bleeding from the endometrium may be under the control of the sympathetic nervous system or other nerve supply. Also, the end-organ—the uterus and its endometrium—will respond differently depending upon its development, just as in the same individual the breasts, whose growth is under the control of the ovarian hormone, may respond to ovarian stimulation by growing to different sizes. The reason for this is not that the ovarian hormone is supplied to each breast in varied amounts, but that each breast, as an end-organ, responds differently to the same stimulation. The underdeveloped uterus and endometrium, as end-organs, may respond poorly to normal amounts of hormones and bleeding may be very different from the bleeding of a well developed organ. It is possible, also, that the response of the blood vessels and their nerve apparatus in individual organs may be abnormal. Bleeding will be greater from an organ with a superior blood supply than from one with an inferior blood supply. The fact that menstruation can be brought on suddenly or may stop because of fright or emotional shock shows that bleeding is not primarily controlled by ovarian hormones but is a nerve or blood vessel phenomenon, or possibly adrenal mechanism. The normal ovary rules the normal endometrium and its normal blood supply, and an abnormal ovary with an abnormal secretion will pervert the bleeding from a normal uterus. An abnormal physiologic state, such as pituitary failure, thyroid failure, starvation or disease will upset menstruation and may do so not because of partial ovarian failure, but because the end-organ and its blood vessels may be disorganized as well as the ovary. The causes of normal menstruation are controlled by a normal ovary, endometrium and blood vessel arrangement, but abnormal menstruation or bleeding or amenorrhea may be due to conditions far removed from ovarian failure. Ovarian failure will upset menstruation but ovarian failure is not the only mechanism that can do it. The most important link in the chain is the control of the neurovascular system. If hormones control this system then hormone failure is most important, but if not, then a search must be made for another control.

NEUROGENIC SHOCK

I. THE EFFECTS OF PROLONGED LOWERING OF BLOOD PRESSURE BY CONTINUOUS STIMULATION OF THE CAROTID SINUS IN DOGS

DALLAS B. PHEMISTER, M.D.,

AND

RUBIN J. SCHACHTER, Ph.D.

CHICAGO, ILL.

FROM THE DEPARTMENT OF SURGERY, UNIVERSITY OF CHICAGO, CHICAGO, ILL.

DURING THE PAST CENTURY AND A HALF, in which the word shock has been used medically to indicate a state of acute circulatory embarrassment or failure associated with wounds, hemorrhage and other accidents, there has existed a marked tendency on the part of the medical profession to consider it brought about somehow through the nervous system.

Psychic activity incident to the accident and resulting in the passage of impulses from the brain to the vasomotor centers in the medulla may play a variable rôle and may be difficult to evaluate. That vasodepressor centers exist in the cerebral cortex was shown recently by Hoff and Green,[1] who produced a decline in blood pressure by electrical stimulation of the lateral, suprasylvian, ectosylvian and sylvian gyri in cats and occasionally the marginal gyrus and a small area of cortex near the anterior tip of the superior precentral sulcus in monkeys. Fainting frequently accompanies a variety of sudden accidents and may send the blood pressure to very low levels.[2] If the reaction is marked and prolonged, as is rarely the case, and if combined with other shock-producing factors such as hemorrhage, it may be of importance in initiating or prolonging a state of shock. Fear has been considered by Freeman,[3] Cannon,[4] and others, to be an exciting factor in shock by increasing the output of adrenalin, producing vasoconstriction with damage to and increase of permeability of capillaries, hemoconcentration, and secondary fall of blood pressure.

Injury to sensory nerves of the traumatized field resulting in afferent impulses to the vasomotor centers in the medulla is the method of action that has been most generally considered. The sensory stimuli are generally assumed to inhibit vasoconstrictor impulses and lower blood pressure although the possibility exists that vasodilator impulses may simultaneously be augmented. The most serious objection to this theory is that while vasodepressor responses may be elicited by electrical stimulation or by mechanical stimulation (as by cutting, pinching or stretching) of cerebrospinal nerves during operations on man or experiments on animals, they are usually absent in most of these instances, and if present are practically never of a degree that results in shock or even in marked and prolonged lowering of blood pressure.

The carotid sinus and cardio-aortic nerves are special afferent modulator nerves for the blood pressure with centers in the medulla and axonal endings in the walls of the blood vessels and in case of the cardiac division of the cardio-aortic nerve in the left heart. Stimulation of these nerves results in lowering of the blood pressure which varies to some extent in degree and duration with the nature, strength and length of the stimulus. The existence of similar modulator nerves has been postulated for other arteries, such as those of the abdomen, but never definitely proven. It has been the general observation that falls of blood pressure often to shock levels (70 Mm. of mercury or under) may usually be produced within a period of one to three minutes by appropriate stimulation of either the carotid sinus or the cardio-aortic nerves. The pressure may be maintained at a low level for an indefinite period or it may rise to varying levels as a result of varying degrees of exhaustion of the reflex. However, no reports have been found in the literature of very prolonged stimulation of these nerves in an endeavor to determine whether or not the blood pressure can be maintained at low levels for a sufficiently long time to become the sole or an important factor in the causation of shock. Freeman[3] lowered blood pressure in five cats by cardio-aortic nerve stimulation maintaining it between 60 and 80 Mm. of mercury for 95 minutes in one case. The accompanying blood changes were negligible and the pressure promptly returned to the original level on removal of the stimulus.

Experiments have been conducted in an effort to determine the effect of continuous and prolonged stimulation of the carotid sinus of the dog and of the cardio-aortic nerves of the rabbit. Also, an attempt has been made to determine whether or not there are similar nerves supplying blood vessels within the abdomen which on stimulation lower the blood pressure. The results of carotid sinus stimulation are reported here.

The vasodepressor effect of stimulation of the carotid sinus was discovered by Hering,[5] and Koch,[6] and has since been considerably elaborated by Heymans and coworkers,[7] and others. Short to medium periods of stimulation in dogs have not been found to bring on a state of shock although sudden reflex death has occasionally resulted during dissection or mechanical or electrical stimulation of the carotid sinus or its nerve.

EXPERIMENTAL METHODS

Dogs weighing from 7 to 15 Kg. were anesthetized with sodium barbital, 300 mg. per Kg. body-weight, intravenously. When smaller doses were tried there was usually struggling and disruption of the set-up especially on electrical stimulation. The experiment was also set up under evipal anesthesia, and the animal allowed to recover. Stimulation then also produced struggling and disruption of the set-up. Kymographic tracings of blood pressure were recorded from a cannula in the femoral artery. Stimulation was produced in some cases mechanically by distention of the carotid sinus, in others electrically by an induced current passing through a bipolar elec-

trode applied to the sinus in one form externally and in another form intravascularly. Erythrocyte counts, hematocrit, and in some cases hemoglobin and serum protein determinations, by the Barber-Hamilton method, were made before and at intervals in the course of the stimulation. Blood was drawn from the exposed femoral vein in most experiments but more recently from the femoral artery.

Mechanical Stimulation.—For mechanical stimulation the technic of Heymans was used. An inverted jugular vein sac was attached to the end of a cannula which was then inserted and tied in the carotid artery, so that the sac rested in the sinus. The external carotid artery was ligated near its origin. By distention of the sac with water the pressure was raised to the desired levels. Sac pressures ranging between 175 and 275 Mm. of mercury were found to give the greatest falls in blood pressure.

There were eight experiments of this kind. Sinus distention promptly lowered the blood pressure to some degree in seven but in only three did the level reach 70 Mm. of mercury or lower. Usually, regardless of the level of descent the pressure began to rise within a few minutes and reached the previous level in from 10 to 40 minutes. After periods of rest there would usually be a response to stimulation of the same character. One dog which showed falls of blood pressure of 20 to 40 Mm. lasting up to 30 minutes, died suddenly when the pressure was released at 120 Mm. mercury. In one dog there was failure of response despite repeated and varied elevations of pressure in the sinus. Section of the vagi in three cases after failure to hold the pressure at low levels by stimulation made little difference in results. The remaining animals were sacrificed after 4 to 13 hours while stimulation was not being carried out. Their blood pressures were at or only slightly below the levels before stimulation was begun and there were no changes in R. B. C. counts or hematocrits, or other evidences to indicate a state of impending or existing shock. The method of stimulation was consequently abandoned as being inadequate.

Electrical Stimulation with Electrode Applied Externally.—In a second group of 14 experiments the region of bifurcation of the common carotid artery was dissected free of surrounding soft parts. One wire of a bipolar electrode was hooked about the internal carotid and the other about the common carotid near the bifurcation. In addition, five animals died suddenly during the dissection in an attempt to carry out this procedure, from reflex respiratory and/or cardiac arrest, it being difficult to say which.

Stimulation was from a Harvard inductorium with 6 to 11 cm. separation of the secondary coil from the zero point. Leakage of current to the surrounding soft parts was troublesome. In 10 experiments there were falls of blood pressure but the degree and duration were very variable. Five animals showed moderate short responses but died suddenly at the onset or within 12 minutes to 2 hours in the course of stimulation, probably from current leakage to the adjacent vagus. Only two dogs had prolonged falls of pressure.

In one, the initial pressure was 150 Mm., and under almost continuous stimulation for 6 hours it ranged between 80 and 100 Mm. and the erythrocytes increased gradually from 6,480,000 to 8,020,000, and the hematocrit from 53 to 59. Death occurred suddenly from vagus arrest of the heart. In a second dog the pressure fell initially from 145 Mm. and fluctuated between 75 and 125 Mm. under continuous stimulation for 11 hours. When the stimulus was removed for ½ to 2 minutes, the pressure always bounded upward to 140–160 Mm. and when released at the end, before killing, it was 155 Mm. The erythrocytes were 6,080,000 and the hematocrit 43 before stimulation. After 5½ hours they were 6,800,000 and 48, respectively. Estimations 10 minutes before the stimulus was stopped showed 12,000,000 erythrocytes (inaccurate ?) and a hematocrit of 60. Thus, despite the fact that the stimulus was removed after 11 hours, the blood pressure rose as high as it was at the beginning, showing that vasomotor control was still normal. Hemoconcentration had developed during the last 4 hours.

Electrical Stimulation with a Cannula Electrode.—In an endeavor to improve the method of stimulation, a bipolar cannula electrode was devised. It is inserted and tied in the common carotid artery, the distal pole being carried into the first portion of the internal carotid leaving the proximal pole in the carotid sinus. The cannula and the method of insertion are shown in Figure 1. For the prevention of leakage of current, the carotid artery is tied and divided proximally, the freed surrounding soft parts retracted by two Farr automatic retractors and one ribbon retractor anchored to a cross bar. The set-up of the experiment is shown in Figure 2. In four experiments, both carotids were cannulated but the results of bilateral stimulation were little different from those of unilateral stimulation.

The results of cannula electrode stimulation in 19 experiments were a great improvement over those obtained by previous methods, as the circulation of the sinus was well preserved, and it responded to stimulation for long periods. By avoiding dissection about the carotid sinus nerve, there was no death during the preparation of the experiments. In every experiment there was at some time a response to stimulation but there was variation in the intensity, duration and time at which it was obtained. With initial blood pressures varying from 110 to 160 Mm. mercury, there was usually a fall at the onset of stimulation with the secondary coil 10 to 8 cm. from the zero point. In the majority of the experiments the pressure fell from 25 to 50 Mm. of mercury, leaving it at suprashock levels and sometimes much stronger stimuli were necessary. However in a minority of cases the fall was to 70 Mm. of mercury, or lower. The most marked falls were usually in animals showing little or no embarrassment of respiration. In experiments giving the most marked and persistent response it was possible to lower the blood pressure to shock levels either immediately or relatively soon after the onset of stimulation and maintain

TABLE I

CAROTID SINUS STIMULATION MAINTAINING BLOOD PRESSURE ALMOST CONTINUOUSLY AT SHOCK LEVELS UNTIL DEATH

Exper. No.	Survival Hours	Stimulation Period Hours	B. P. Mm. Hg.	Pulse Rate	Respiration	R. B. C. Millions	Hematocrit %	Pathology
		0	110	120	20	7.14	48	Lung: Congestion of capillaries and venules, little hemorrhage and protein precipitate in alveoli. Liver: Extreme stasis in both hepatic and portal systems. Liver cords either vacuolated or granulated in places. Some lymphatics markedly distended with lymph coagulum. Kidneys: Marked congestion and acute granular degeneration of epithelium of tubules. Adrenals: Marked congestion, some hemorrhage and degeneration of cells of fasciculate zone. Little cortical and medullary change. Lymphatic ganglion near adrenal: Extensive degeneration of nuclei of some cells. Changes in other viscera negligible.
		0.1	66					
		1.0	60	124	24	7.14	47	
114	7.5	2.0	50	142	20	7.52	51	
		3.5	70	138	28	8.72	57	
		5.5	70	134	22	9.60	61	
		7.5	35			9.14	59	
		0	130	120	16	5.44	37	
		0.2	76					
119	9.5	1.0	100	116	22	7.28	40	
		2.5	74					
		3.5	83	96	8	7.12	40	
		6.5	65	84	8	6.88	39	
		9.25	44	132	7	6.08	39	
		0	106	126	36	5.28	33	Necropsy: Moderate edema and atelectasis of lungs. Aspirated vomitus in some bronchi. Central congestion and slight granular degeneration in cords of liver lobules. Slight degeneration of fasciculate zone of adrenal cortex. Nuclear degeneration in convoluted tubules of kidneys. Spleen small and anemic, as in collapse. Other visceral changes negligible.
		0.1	50					
		1.0	74	120	20	5.76	30	
129	8	3.0	70	140	28	7.56	39	
		6.25	75	136	26	7.36	36	
		7.75	44	144	48			

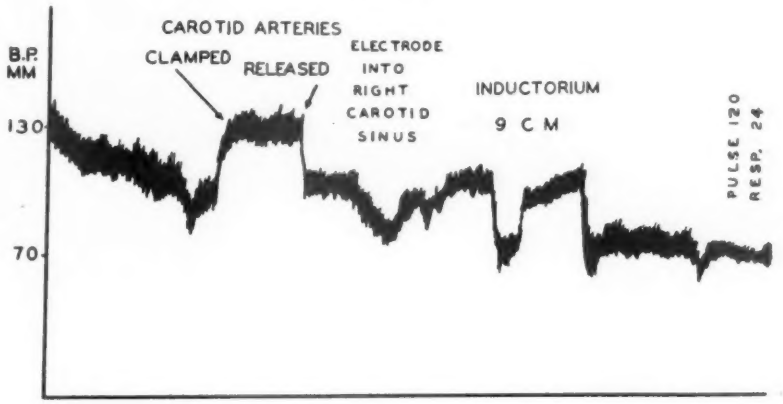
Average 8.3

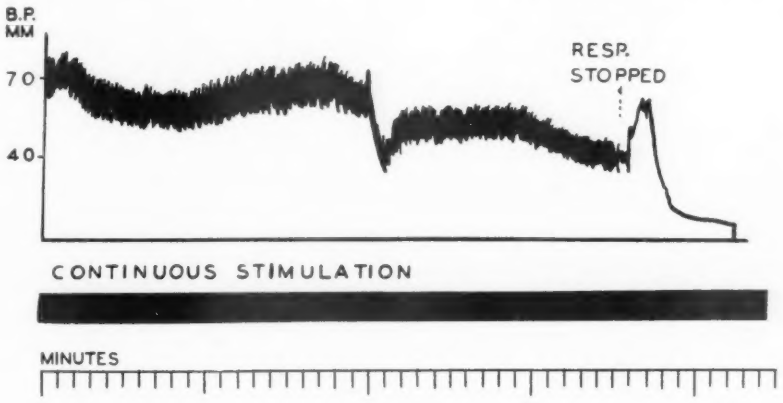
it continuously or almost at such levels until circulatory exhaustion and death occurred. A summary of the results of three experiments is given in Table I.

The average survival time after beginning the continuous stimulation was 8.3 hours. As the blood pressure gradually declined there was a tendency to hemoconcentration as shown by the erythrocyte counts and the hematocrit. This was slight in Experiments 119 and 129. Necropsy in Experiments 114 and 129 revealed congestion and acute degenerative changes in most of the viscera. The hemoconcentration and pathologic changes were most marked in Experiment 114, in which the blood pressure was most consistently at low levels, and in which death occurred earliest after 7.5 hours. Graph 1 shows the early blood pressure tracing with the rise and fall of pressure from clamping and releasing the common carotid arteries, the fall of pressure from short stimulation with the inductorium at 9 cm. and the early part of the prolonged period of continuous stimulation. Release of the stimulus for 2 minutes three hours after the beginning with a pressure of 62 Mm. of mercury resulted in a rise of 30 Mm. However, a similar release 55 minutes before death resulted in only an 8 Mm. rise in pressure, showing that the circulation was so badly damaged that an almost irreversible

state was present. Graph 2 shows the further decline during the final 35 minutes of life. Photomicrographs show the blood and lymph stasis in the liver (Fig. 3), the cell necrosis in the convoluted tubules of the kidney (Fig. 4) and the disappearance of nuclei in sympathetic ganglion cells (Fig. 5).

GRAPH 1.





GRAPH 2.

GRAPH 1.—Experiment 114: Showing carotid sinus reflex from clamping and releasing carotid arteries and electrical stimulation of right carotid sinus.
GRAPH 2.—Experiment 114: Blood pressure tracing before death, following 7½ hours of stimulation, with maintenance at shock levels.

In the larger group of experiments in which, for a long period, the reduction in blood pressure was to irregular suprashock levels, the general effect on the animals was relatively slight, and on release of the stimulus the pressure would mount to approximately the prestimulation levels. At times

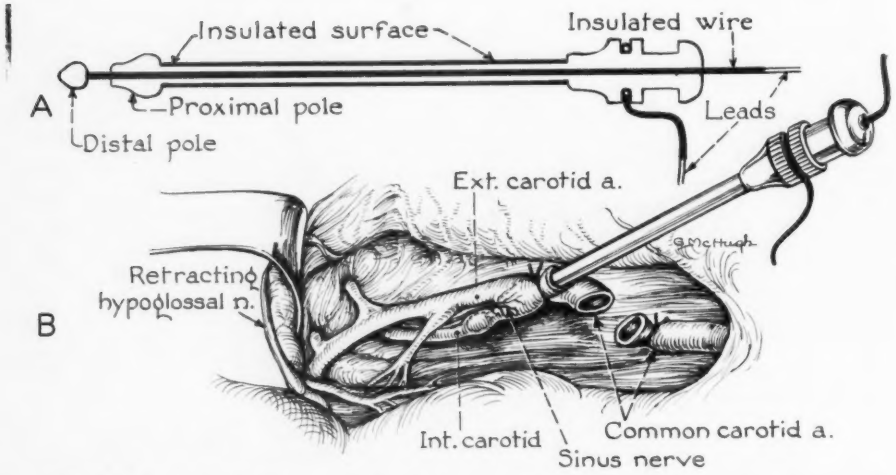


FIG. 1.—A. Insulated bipolar cannula electrode. B. Electrode inserted through right carotid artery with distal pole in internal carotid artery and proximal in carotid sinus.

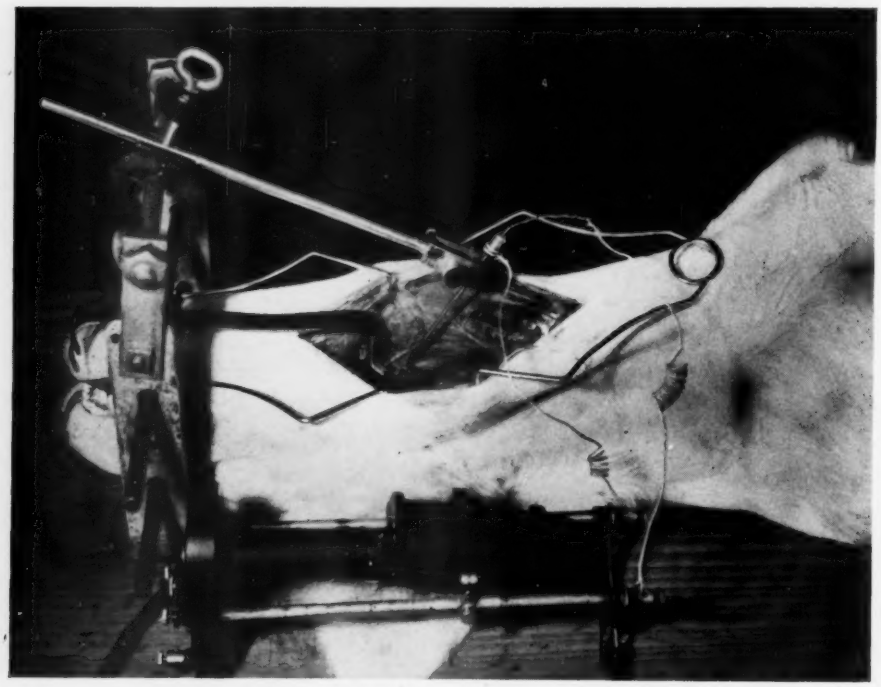


FIG. 2.—Experiment set-up for stimulation. Cannula inserted in carotid sinus and held in the clear by clamp. Surrounding soft parts retracted by one anchored ribbon retractor and two Farr automatic retractors.

the reflex would be exhausted and the pressure would rise to previous levels. Following a brief rest period, the pressure would again fall on stimulation.

TABLE II

BLOOD PRESSURE LOWERED TO SUPRASHOCK LEVELS DURING ABOUT THE FIRST TWO-THIRDS OF PERIOD OF CAROTID SINUS STIMULATION

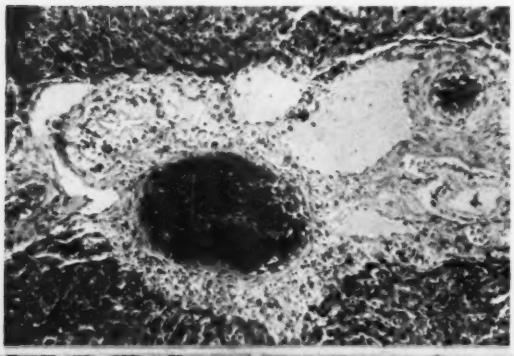
Exper. No.	Survival Hours	Time Hours	B. P. Mm. Hg.	Pulse Rate	Resp. Rate	R. B. C. Millions	Hemato-crit %	Pathology
		0	120	138	16	6.96	35	Operative wounds infected. Marked hypostatic congestion of lungs. Some blood in alveoli. Lymphatics distended with coagulum. Central venous engorgement in liver with degeneration in adjacent cords. Some degeneration in cortical zone and degeneration and hyperemia in fascicular zone of adrenals. Extensive degeneration and sloughing of convoluted tubules of kidney. Moderate hyperemia of kidney and spleen. Subepicardial vascular engorgement, with lymphatics distended by lymph coagulum. Slight waxy degeneration of myocardium. Pancreas, jejunum and skeletal muscle normal. Some degeneration in peripancreatic sympathetic ganglion.
		0.3	80					
		0.6	80	128	20	5.52	31	
131	26	1.6	90	136	20	5.78	35	
		2.6	100	168	20	5.48	34	
		5.0	84	162	28	4.32	26	
		9.0	82	176	26	3.84		
		13.0	80	150	36	5.68	35	
		(over night)						
		22.5	72	172	28	6.4	39	
		24.6	68	170	28	6.24	40	
		25.6	45			5.59	41	
		0	170	180	22	9.04	48	Operative wounds infected. Hypostatic congestion and beginning pneumonia in posterior lobe of lung. Passive congestion of liver and degeneration of cord cells. Acute necrosis of cells of convoluted tubules and marked congestion of kidney. Congestion and moderate degeneration in intermediary zone of the adrenals. Pancreas, spleen, jejunum and skeletal muscle normal. Some fragmentation of myocardial fibers.
		0.1	140					
		1.0	140	168	20	8.96	55	
132	14.75	1.2						
		1.65	128					
		3.0	135					
		4.0	85	160	24	9.76	51	
		6.5	90	180	16	10.38	53	
		9.0	90					
		9.5	90	184	28	9.68		
		10.0	70					
		13.0	54	160	24	9.14	51	
		0	130	138	24	6.90	47	Operative wounds infected. Hypostatic congestion and slight atelectasis of lungs. Engorgement of central lobe veins and necrosis of cords of liver. Slight hyperemia and necrosis of tubules of kidney. Moderate hyperemia, necrosis and leukocytic infiltration of intermediary zone of adrenals. Other viscera and cardiac muscle essentially normal.
		0.25	90					
		1.0	98					
133	18.3	2.0	100	160	28	8.00	51	
		4.5	115	168	32	7.44	45	
		9.0	110	176	19	6.56	44	
		9.75	105					
		11.5	80			8.40	44	
		15.5	70	144	24			
		16.5	60	144	32	7.28	46	
		18.0	25	160	16	6.72	42	

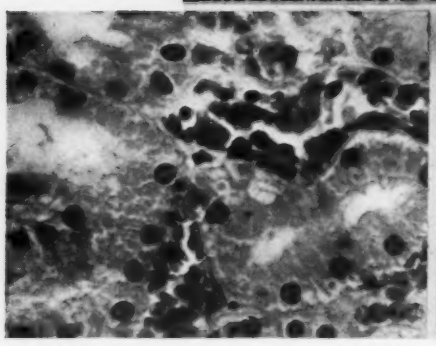
Average 19.7

However, after 10 to 20 hours of continuous, or almost continuous stimulation, the blood pressure would decline to shock levels and then death would result in a shorter time than in the animals whose pressures fell to shock levels at the onset of the stimulation. The results of three experiments are given in Table II.

The average survival period was 19.7 hours. There was relatively little fluctuation in the erythrocyte counts and hematocrit, either before or after the blood pressure descended to shock levels. The experiments ran long enough for wound infection to be established and to play a part in the causation of death.

FIG. 3.





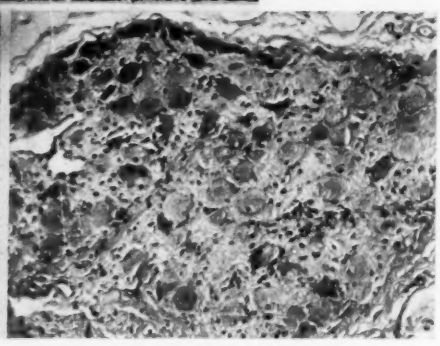
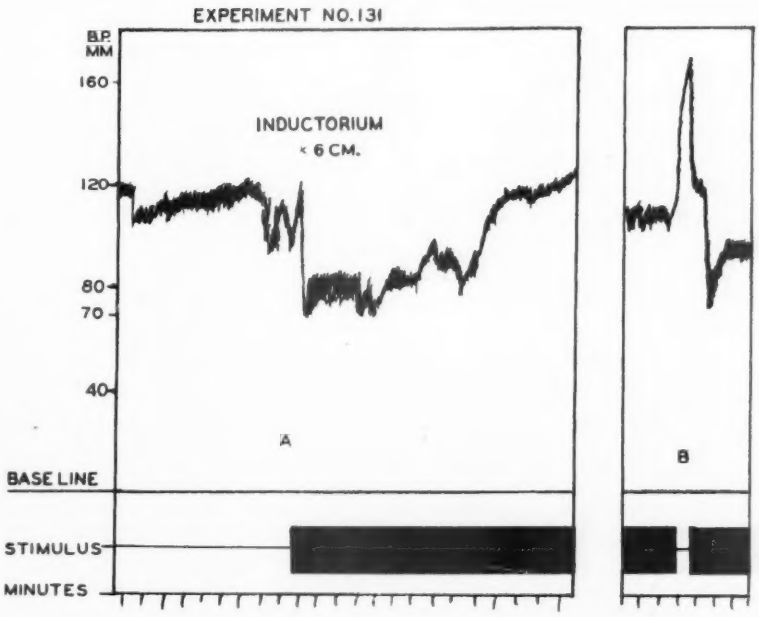


FIG. 4. FIG. 5.

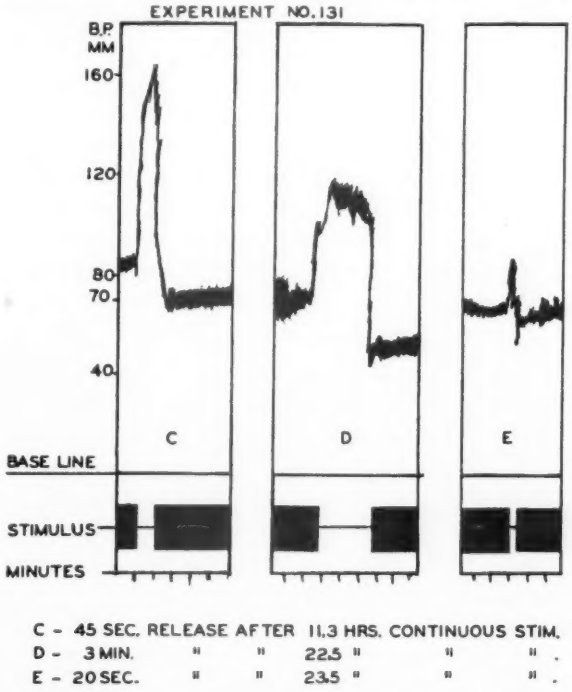
FIG. 3.—Experiment 114: Engorgement of veins and capillaries with blood, and of lymphatics with lymph coagulum.
FIG. 4.—Experiment 114: Necrosis of cells of kidney tubules.
FIG. 5.—Experiment 114: Necrosis of cells of sympathetic ganglion.

In Experiment 131 the animal lived 26 hours. The duration and degree of fall during the first 13 hours varied considerably. Graph 3 shows the decline of pressure on initial stimulation with the inductorium at 6 cm. and the rapid return to a higher level despite continuation of the stimulus. After moving the secondary coil to 4 cm. the pressure again fell and with that strength unchanged it remained at irregularly low levels until death. During the long period that the pressure remained at suprashock levels, the rise of pressure on temporary release of the stimulus was very marked as shown at the end of 3.2 hours by Graph 3b, and at the end of 11.3 hours and 22.5 hours as shown by Graph 4c and d, respectively. However, after the pressure had been at shock levels for one hour, the elevation of pressure on release was very slight (Graph 4e) and after another hour it failed to occur.

For comparison with these two groups of stimulation experiments, a third or control group was run, in which the procedure was the same except the electrical stimulus was not applied to the sinus. The results are shown in Table III. The average duration of life was 28.7 hours. The blood pressure did not drop to shock levels until an average of about 4 hours before



GRAPH 3.—Experiment 131: A. Showing fall in blood pressure to suprashock levels, with recovery during carotid sinus stimulation. B. Elevation of blood pressure on release of stimulus, while pressure is maintained at suprashock level for 3.2 hours.



GRAPH 4.—Experiment 131: Showing marked pressor response on release of stimulus after maintenance at suprashock levels for (C) 11¾ hours. Response still good when shock level reached (D) after 22½ hours, but feeble (E) after 23½ hours.

TABLE III

CONTROL EXPERIMENTS FOR CAROTID SINUS STIMULATION

Exper. No.	Survival Hours	Time Hours	B. P. Mm. Hg.	Pulse Rate	Respiration	R. B. C. Millions	Hematocrit %	Serum Proteins	Pathology
		0	145	88	28	9.60	56	5.61	Necropsy: Early infection of wounds. Early pneumonia. Early necrosis of many cells of convoluted and collecting tubules of kidneys. Central congestion of liver lobules, degeneration of liver cells. Degeneration and nuclear fragmentation of adrenal cortex. Slight waxy degeneration of heart muscles. Other viscera and skeletal muscle showed no changes.
134	26.35	2.3	150	180	24	9.12	60	5.48	
		8	150	205	24	10.24	60	5.78	
		10.25	140			10.32	57	5.61	
		(over night)							
		22	80	88	12	8.72	53	5.48	
		24	70	138	20	8.88	54	5.48	
		26	40			8.80	52	5.65	
		0	160	180	22	7.76	51	5.58	Necropsy: Moderate atelectasis and congestion of lungs. Degeneration of glomerular zone and of cells of cords of adrenal cortex. Slight degeneration and sloughing of cells of convoluted tubules of kidney. Congestion of liver lobules. Other viscera show no change. Infection of wounds.
135	31	2	160	180	20	7.84	53	6.26	
		8	160	180	20	8.64	54	6.35	
		14	130	170	28	8.08	50	6.22	
		20	90	144	10	8.16	52	5.65	
		25	70	150	12	7.68	49	under 5.58	
		30	50	164	10	6.90	48	under 5.58	
									Hb.
		0	120	144	24	5.68	45		84 Hypostatic congestion of lungs and early pneumonia. Necrosis of cells of tubules of kidneys. Hyperemia. Necrosis and leukocytic infiltration of intermediary zone of adrenal. Marked engorgement of liver veins and necrosis and leukocytic infiltration of liver cells. Other viscera and skeletal muscle show negligible change. Infection of experimental wounds.
187	29	1.6	110	140	40	6.08	47	5.31	86
		4	126	160	44	5.84	50	5.48	85
		8	120	180	44	6.80	49		92
		12	100	180	48	6.94	49	5.48	96
		(over night)							
		20	86	190	36	7.20	49	5.24	102
		24	80	180	54	7.68	49	4.97	104
		28	60	160	88	6.72	47	5.24	95

Average 28.7

death. There was no significant change in the erythrocyte counts, hematocrit or plasma proteins. Infection of the operative wounds was more marked than in the group of cases represented in Table II.

DISCUSSION.—The factors to be considered in the causation of death of the animals in which the carotid sinus was stimulated electrically, with the use of the bipolar cannula electrode, are the effects of the stimulus, the anesthetic, the experimental wounds, and the possible late complications from infection and dehydration.

In the group of animals represented in Table I, in which the blood pressure was maintained at shock levels during nearly all of the period of stimulation, there was death after an average of 8.3 hours, with a tendency to hemoconcentration, which was marked in one case and slight in the other two cases. In the two necropsied cases there were acute congestive and degenerative changes in the cells of parenchymatous organs compatible with changes resulting from low blood pressure and failure of the circulation. The anesthetic produced sound narcosis, but there was no evidence that it was an important factor in the cause of early death. The experimental wounds were made with very little blood-loss, and death occurred before there was time for the appearance of toxic effects of their infection. Consequently, it

appears justifiable to conclude that the prolonged maintenance of the blood pressure near or below 70 Mm. of mercury was the most important factor in the production of death from acute circulatory failure.

In the group of animals represented in Table II, in which, during continuous or almost continuous stimulation, the blood pressure remained depressed but at irregular levels, above 70 Mm. of mercury, the animals did not present a tendency to hemoconcentration, and on temporary release of the stimulus, the blood pressure quickly rose to high levels over a period of 10 to 20 hours. Finally, the blood pressure sank to 70 Mm. or below, after which the animals died in an average of four to five hours showing a slight tendency to hemoconcentration during the period. Infection, prolonged anesthesia, and dehydration appeared to be the most important lethal agents and circulatory damage from lowering of blood pressure to suprashock levels by sinus stimulation was of much less significance.

In the third group of control experiments, which lived on an average of 28.7 hours, the prolonged anesthesia and infection of the wounds, and of the respiratory tract were the factors of greatest importance in causing death. The blood showed little change, with a slight tendency to hemodilution, and the blood pressure fell to low levels late in the course of the experiments.

SUMMARY

By electrical stimulation of the carotid sinus in dogs under sodium barbital anesthesia using a bipolar cannula electrode, it was possible to maintain the blood pressure at reduced levels for long periods of time and to observe the effects of the lowered blood pressure upon the body and the general circulation.

In one set of experiments, in which the pressure was held continuously or nearly so at 70 Mm. of mercury or below, the blood became concentrated and death occurred after the lapse of an average of 8.5 hours. At necropsy, there was congestion and acute necrosis of the cells of many of the viscera, and the picture was compatible with shock produced principally by the vasodepressor nerve stimulation.

In a second set of experiments, in which the pressure was lowered by stimulation but remained above 70 Mm. of mercury, there was relatively little damage to the circulation for many hours, as revealed by the absence of hemoconcentration and by prompt elevation of the pressure on temporary release of the stimulus. Finally, the pressures fell to shock levels, and death then followed in 4 to 5 hours with a total survival period averaging 19 hours. The anesthetic and the infections of the wounds and of the respiratory tract were important factors in the causation of death. However, that death was hastened by the blood pressure lowering effects of the stimulation is indicated by the fact that a set of control animals lived an average of 28.7 hours, or 9 hours longer than those of the second group, dying mainly from the effects of anesthesia and infection.

While neurogenic shock has been produced by carotid sinus stimulation

in anesthetized dogs it has only indirect bearing on human shock, since similar stimulation would scarcely be encountered as a result of injury or during operation in man.

The pathology of the experiments has been kindly reviewed by Dr. Eleanor Humphreys.

REFERENCES

[1] Hoff, E. C., and Green, H. D.: Cardiovascular Reactions Induced by Electrical Stimulation of the Cerebral Cortex. Amer. Jour. of Phys., **117,** 411, 1936.

[2] Phemister, D. B., and Livingstone, H.: Primary Shock. ANNALS OF SURGERY, **100,** 714, 1934.

[3] Freeman, N. E.: Mechanism and Management of Surgical Shock. Penn. Med. Journ., **42,** 1449–1452, 1939. *Idem:* Decrease in Blood Volume after Prolonging Hyperactivity of the Sympathetic Nervous System. Amer. Jour. of Physiology, **103,** 185, 1933.

[4] Cannon, Walter B.: A Consideration of Possible Toxic and Nervous Factors in the Production of Traumatic Shock. ANNALS OF SURGERY, **100,** 704–713, 1934.

[5] Hering, H. E.: Wien. med. Wchnschr., **73,** No. 16, 729, 1923.

[6] Koch, E.: München. med. Wchnschr., **70,** 1316, 1923. *Idem, ibid.,* **71,** 704, 1924.

[7] Heymans, C., Bouckaert, J. J., and Regniers, C.: Le sinus Carotidien et la Zone Homologue Cardioaortique. G. Doin et Cie., Paris, 1933.

THE STADER REDUCTION SPLINT

FOR TREATING FRACTURES OF THE SHAFTS OF THE LONG BONES

KENNETH M. LEWIS, M.D., LESTER BREIDENBACH, M.D.,
NEW YORK, N. Y.

AND

OTTO STADER, V.M.D.
ARDMORE, PA.
FROM THE FOURTH SURGICAL DIVISION, BELLEVUE HOSPITAL, NEW YORK, N. Y.

IN 1931, one of the authors (Stader[4, 5, 6, 7]) working in the field of veterinary surgery, was impressed with the inadequate methods then in vogue for treating fractures of the shafts of the long bones in dogs. Plaster encasements were not tolerated by the canines, who frequently destroyed them by constant biting and tearing, or the plaster disintegrated by constant soiling and softening with body excretions. Traction and counter-traction were obviously unsuited and although a modified Thomas splint had been used extensively, the degree of fixation obtained was usually insufficient and pressure necrosis from the ring often defeated its continued use. It was thus that Stader, using two half-pin units in each fragment, bridged by a metal adjustable connecting bar, was able to accurately reduce the fracture and allow the apparatus to remain in place and act as a splint. Anatomic reduction could usually be obtained by means of the adjustment on the splint, and because of its compact size it did not seem to annoy the dog and was well tolerated by the animal until union of the fracture had occurred.

In the human, Schanz[1, 3] had described the use of half-nails and screws as a means of skeletal control, and Riedel[2] had suggested an external plate bridging two or more screws or nails, thus permitting firmer fixation. These authors further pointed out the advantages obtained in inserting the pins at an angle to each other (not parallel) as a means of firmer control over the bone fragments. Anderson made use of this principle in his work. Until 1931, all of these men finally fixed the pin assembly in plaster, incorporated as a circular plaster encasement.

Stader gradually used his splint in dogs with greater and greater frequency, and up to the present time (May, 1942) over 1200 fractures in dogs have been treated by this method. The results obtained have been uniformly good and far superior to the older methods of treatment.

In 1937, the two other authors of this paper (Lewis and Breidenbach) had the opportunity of seeing the application of the Stader splint in a police dog with a fractured shaft of the femur. The ease of application, the prompt and accurate reduction obtained, and the simplicity of the instrument made a distinct impression. In addition, the fact that the apparatus would act

as a splint during the ensuing weeks while union was taking place, seemed a decided advantage.

It was then decided to have a larger model of the splint manufactured for use in the human. This was done and, in October, 1937, the first patient was treated by this method on the Fourth Surgical Division of Bellevue Hospital. The patient, W. W., had a fracture of both bones of the leg, and after application of the splint he was bearing weight on the injured limb in two weeks, and walking without the aid of crutches or cane in three weeks. Impressed by the ease of reduction and the possibilities of early weight-bearing without immobilizing either of the adjacent joints, further trial of the splint in fractures of the shafts of the long bones in the human was carried out. Since 1937, a total of 20 patients have been treated by this method. The results have been uniformly good, except in three patients where infection around one or more of the pins occurred. In these cases the infection promptly subsided when the pins were removed. No osteomyelitis has been observed, except in the femur case described below, although in some patients the apparatus has been on for from 14 to 16 weeks. It has been our custom to keep the splint on until bony union has occurred, and this has varied from 8 to 16 weeks. Most of the cases have been fractures of the shafts of both bones of the leg (tibia and fibula), as will be seen in Table I. One fracture of the shaft of the femur was treated in an old man of 84. This case unfortunately succumbed, and because of the patient's age should not have been selected for a trial of the method. Some seepage around the pins, appearing between the 4th and 6th weeks, and due to galvanism between the bone and pin has been seen. This has been largely overcome since the pin bar has been made of a plastic instead of a metal. When it does occur, however, it is not of significance and promptly subsides after the splint and accompanying pins have been removed at the end of treatment.

DESCRIPTION OF MECHANICAL PARTS AND FEATURES OF THE STADER REDUCTION SPLINT

The mechanical features of the reduction splints are detailed in Plate I, Figures 1 and 2.

The stainless steel pins (A) are made of a special alloy which is resistant to corrosion when embedded in tissue. These pins have been permitted to remain *in situ* for as long as nine months, and upon removal were found completely free from any corrosion. The sharpened end is similar to the end of a trocar, while at the other end, there is a flat surface for the set screw of the pin handle.

In the procedure of applying the instrument, the pins are placed through the desired holes in the pin bar (B) and locked by means of a set screw (C). There are four holes (K) in each pin bar—the two extra ones being for the purpose of selection.

If there is a short fragment on one end of the fracture, it may be necessary to use the two pin holes nearest to each other, while on the long fragments, the pin holes farther away from each other may be desired. The two pins, when inserted through the pin bar, form an angle, and it is by this means that a definite contact is established to the bone. One of the pin assemblies (pin and bar) is placed above the fracture and another below the fracture.

These two pin bars are then abridged by the extension bar by means of the hinge bolts (D) being inserted through the large central hole in the pin bar and tightened by means of nuts (E). In order to overcome overriding of the fragments, the extension bar (F), which is in effect a turnbuckle, is activated by a wrench in such a manner as to cause the pin bars to travel away from each other.

By manipulation of the screws (H) which contact the pin bar from above, accurate alignment of the fragments in the mediolateral plane can be accomplished. Nut (E) should be slightly loosened before the adjustment is made.

By manipulation of the screw (I) each pin bar assembly and fragment can be accurately aligned in the anteroposterior relationship.

By activating the above mentioned adjustments, each fragment can be manipulated in each and every plane.

After the adjustments have been completed and checked roentgenologically, the lock nuts (G) on the extension bar are tightened firmly against the hinge block (L). This locks the instrument for both extension and rotation. The nuts (E) on the hinge bolt (D) are now firmly tightened and then the set screws (I) are firmly set, which locks the remainder of the instrument. The reduction instrument now assumes the rôle of a splint.

In order to reduce the weight of the instruments, most of the parts are made of duralumin; those parts absorbing great strain are made of stainless steel.

Before going into the detail of surgical procedure, it might be well to take up a few general considerations, in order to picture to the reader a few of the fundamentals in the use of the Stader reduction splint. If one refers to Plate I, Figures 1 and 2, it will be seen that the pin assemblies are placed as near the extremities of the bone as possible. This is exceedingly important and should be constantly kept in mind. The reasons for placing the pin assemblies close to the bone extremities are:

1. The first principle in treating a fracture of the shaft of the bone is to correct the overriding. Overriding is caused by muscular contraction. As the muscles causing the overriding, for the most part, have their origin and insertion at or near the bone extremities it seems logical to inactivate them at these points. When these muscles are inactivated in this manner they cannot produce unusual strains upon the instrument or the bone fragments which they control.

2. Some of the serious objections to placing the pin near the point of fracture are:

(a) They are introduced into the traumatized tissue which is devitalized in many instances.

(b) When the pin assemblies are placed close to the point of fracture the muscle groups have a greater purchase upon the fracture bone fragments, by virtue of the fulcrum produced by the instrument. This, then, throws greater stress upon both the instrument and the fractured bone. In other words, one tends to hold the fracture in place by brute force.

(c) When the pin assemblies are placed close to the fracture it is more difficult to successfully reduce the fracture because of the previously mentioned muscular action upon the extremities of the bones.

The following mental conception of the problem may be useful. Normally an unfractured bone is situated in a muscular furrow. Now, by applying the apparatus near the extremity of the bone fragments, the fragments tend to float within this furrow during the reduction maneuvers. In this way all forces under extension tend to assist in reducing the fracture.

ACTUAL SURGICAL PROCEDURE OF APPLYING THE STADER REDUCTION SPLINT

Careful skin preparation is essential, and the same surgical aseptic safeguards should be observed as in any surgical procedure on bones. The splint should only be applied in the operating room, and careful sterilization is of course necessary.

Placement of the Pins.—As a general rule the upper pin assembly is placed first. Place one of the pins into the pin handle or in a flexible shaft drill and tighten it firmly into place with the set screw. Introduce this pin through the desired hole in the pin bar and then hold this assembly in the right hand. With the left hand, accurately determine the point for pin No. 1 to enter. Steadying the area with the skin stretched toward the fracture by the left hand, the right hand introduces the pin and by firm, steady pressure forces the pin through the skin and soft tissues on to the outer cortex of the upper fragment of the bone.

By firm pressure and rotation, the pin is firmly seated into the outer cortex. Then, by deep palpation upon the medial side of the limb the upper fragment is steadied while the pin bar is brought into *parallel alignment* with the long axis of the upper fragment by means of slightly altering, if necessary, the angle of introduction of the pin which up to this point has only been seated. After the upper fragment and pin bar have been brought into parallel alignment, continued pressure and rotation of the pin handle will introduce the pin through the outer cortex, through the medullary canal, and then through the inner cortex. Care should be exercised so that the pin-points definitely emerge through the inner cortex. This can be ascertained by a gradual release of resistance as the pin points start to emerge,

as well as by deep digital palpation which will frequently reveal the pin-points through the inner cortex.

The insertion of the pins is difficult in some instances, especially so where the cortex of the bone is unusually thick. If this difficulty is met with, drilling a hole with a bone drill slightly less in diameter than the pins to be used, will overcome the problem. The pin is then introduced through the tract of the drill, after the drill has been withdrawn.

When using a drill it must be passed through the pin block in order that the hole being drilled will assume the proper angle. The drill should

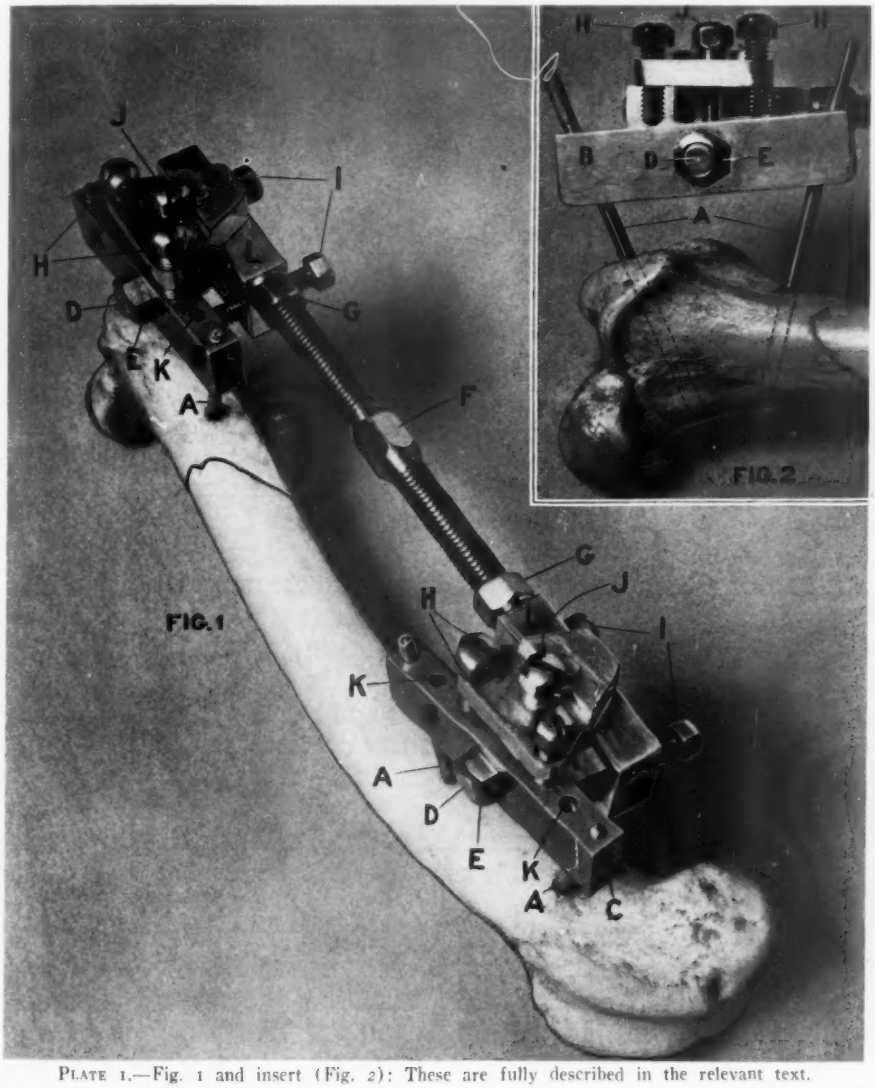


PLATE 1.—Fig. 1 and insert (Fig. 2): These are fully described in the relevant text.

seat well into the distal cortex and when the pin is inserted it should be forced through the opposite cortex by pressure and rotation.

An alternate method is to insert the pin into a Magnuson motor-driven drill handle, adapted to receive the pin. No preliminary drilling is required, but care must be taken to see that the pin is not driven too far through the distal cortex.

If, in the first roentgenograms taken after the instrument has been applied, it is found that the pins project through the distal cortex too far into the soft parts, they can be withdrawn to the proper depth.

As soon as the first pin has been inserted, the handle is unlocked from the pin and another pin fitted into the handle. The second pin is then introduced through the proper pin hole in the same pin bar while an assistant raises the pin bar about one-quarter of an inch above the surface of the skin. The second pin is then applied in a similar manner as the first, emerging through the inner cortex as above described.

The second pin assembly is then placed in position. When all four pins have been placed, they should be locked with the small hexagonal wrench by means of set screws in the end of each pin bar.

Applying the Extension Bar.—Adjusting screws I and H should be unscrewed so they will not interfere with slipping the extension bar on to the pin bars. Lock nuts G on extension bar should be loosened so as to facilitate extension or contraction as well as rotation. From a strictly mechanical point of view there is no reason why, if one had two inches of overriding in a given fracture, the extension bar could not be so adjusted that it would slip onto the pin bars with this degree of overriding being present, with the idea of then proceeding to overcome shortening and then the other types of displacements. From experience, however, it has been shown that much time can be saved if the operator will grasp the pin assembly in each hand and manually overcome as much of the overriding as possible, before applying the lateral extension bar. In this way fully 75 per cent of the reduction maneuvers will be accomplished in 30 seconds time. While the operator maintains this position (Fig 3) the assistant adjusts the extension bar to the right length and slips the stud bolts (D) through the holes in the pin bar and then proceeds to screw on the nut (E). Before the operator lets go of the pin bar assemblies, the adjusting screws I and H are snugly set with the fingers only.

Extension.—By properly manipulating extension bar nut (F) the proper degree of extension can be easily secured. This can be checked in many instances by deep palpation.

Mediolateral Alignment.—A mediolateral alignment of either segment is secured by proper manipulation of adjusting screws H. Obviously, when this adjustment is being made, nut E should be slightly loosened. After it has been secured, nut E should be firmly tightened.

Anteroposterior Alignment.—Each segment can be manipulated in this plane by set screws I. The patient is then moved to the Radiologic De-

partment, where final manipulations are accomplished either under fluoroscopic guidance or by taking several roentgenograms.

The question has often been asked as to whether the pins should be put in place with the aid of the fluoroscope? The answer is definitely "No."

1. Too much fluoroscopy would be necessary, which would endanger the patient and the operator.
2. By having an accurate knowledge of the anatomy involved, fluoroscopic guidance is unnecessary.

FIG. 3.—Showing pins and pin bars in place; and extension bar about to be applied.

3. Sterile surgery is impractical in the Radiologic Department.

A very important factor in the treatment of fractures is to see that firm impaction of the fragment is secured. As a final adjustment it is well to slightly impinge the fragmented ends upon each other.

By firmly setting all adjusting screws, the entire instrument becomes locked and now acts as a splint.

CASE REPORTS

Four typical cases are reported in some detail. These were selected at random but illustrate some of the advantages of the Stader splint.

Case 1.—N. W., age 22, was admitted to Bellevue Hospital, March 16, 1941, with an oblique fracture of the right tibia and fibula. A plaster encasement was applied, March 16, 1941, and the postreduction film showed excellent position. He was discharged, March 19, 1941, with crutches, but without bearing weight. On April 2, 1941, he returned complaining of severe pain in the leg. Roentgenograms showed what usually happens to an oblique fracture of the tibia and fibula when put in a plaster encasement

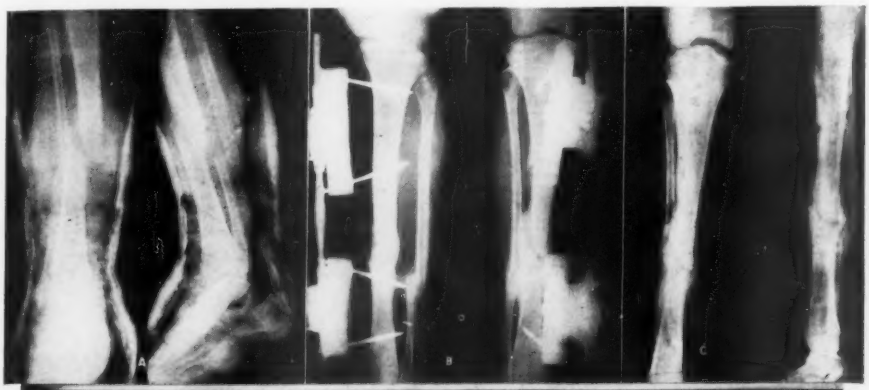
FIG. 4.

FIG. 5.

FIG. 4.—Showing a dog with a fracture of the femur—Stader splint in place.
FIG. 5.—A. and B. Splint in place. C. Splint removed—pin holes healing.

before union occurs. Overriding and some angulation had developed and a good weight-bearing leg was improbable. On April 2, 1941, the encasement was removed and a Stader splint applied. The position of the fragments was excellent and walking was started within a few days. On April 11, 1941, he returned to work and continued working with no loss of function of his leg and no complaints. There was no seepage from any of the pins. On June 9, 1941, he had firm and solid union roentgenologically.

FIG. 6.



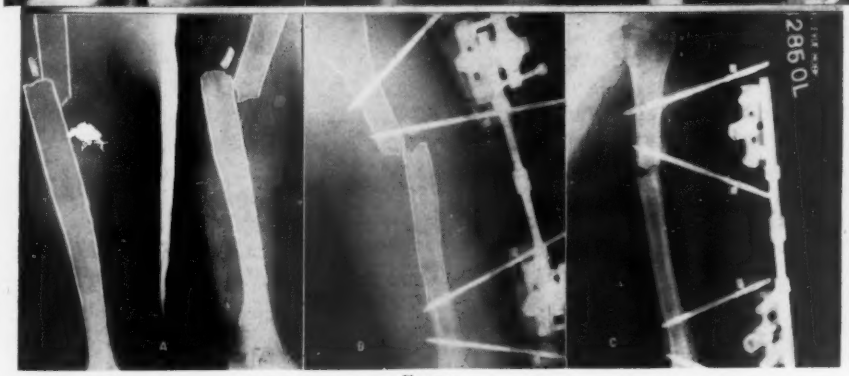


FIG. 7.

FIG. 6.—Case 1: Fracture of Tibia and Fibula. A. Malposition in plaster. B. Apparatus in place—fracture reduced. C. Showing union—apparatus removed.
FIG. 7.—Case 2: Fracture of Shaft of Humerus. A. Before reduction. B. Apparatus in place but fracture not completely reduced. C. Reduction completed after return to the ward.

The splint was removed. No further treatment was necessary. Three days later the dressings on the pin holes were removed and complete healing occurred within a week. This was an ideal case in that, with complete cooperation, he lost no time from his work and union occurred in an exceptionally short period of time (Fig. 6).

This case demonstrates several points:

(1) An oblique fracture cannot be adequately immobilized in a plaster encasement. In our experience, slipping of the fragments frequently occurs.

(2) The fracture, in spite of being two weeks old, could still be reduced with the Stader apparatus.

(3) Union occurred rapidly, with the firm immobilization that this apparatus afforded.

Case 2.—G. G., male, colored, age 47, was admitted to Bellevue Hospital, December 26, 1937. He had sustained a fracture of the left humerus shortly before admission, with musculospiral nerve paralysis. A Stader apparatus was applied, and excellent reduction obtained. The splint was removed, March 5, 1938, and the arm placed in a sling. The pin holes healed promptly, and he was discharged, March 16, 1938, with a cock-up splint to correct a wrist drop. On March 21, 1938, examination showed firm union at the site of fracture and the pin holes healed. The wrist drop was treated with cock-up splint and galvanic current therapy. On June 20, 1938, the musculospiral paralysis had almost entirely cleared. He had full function of the elbow and shoulder joint, and has remained well and returned to work, with no symptoms (Fig. 7)

This case shows the usefulness of the Stader apparatus in fractures of the shaft of the humerus.

Case 3.—A. D., white, male, age 36, was admitted to Bellevue Hospital, August 30, 1941. He had been hit by an automobile just before admission, and sustained a badly comminuted compound fracture at the junction of the lower and middle thirds of the tibia and fibula. The wound was adequately débrided, under general anesthesia, and a Kirschner wire was inserted through the oscalcis, and skeletal traction was applied. On September 2, 1941, a posterior molded plaster splint was applied while in traction, and the traction maintained Three weeks later a circular plaster encasement was applied over the posterior molded splint, after packing the compound wound with vaselined gauze. The traction was discontinued. Roentgenograms showed good alignment and the patient was discharged walking on crutches. He was readmitted to the hospital on three occasions for change of encasement due to the profuse discharge and odor. The wound was freshly packed with vaseline gauze at each admission. The roentgenograms showed the same good position but never any evidence of callus formation nor any evidence of wound-healing. At the end of seven months, in March, 1942, roentgenograms showed no callus, and the wound was draining a large amount of pus. It was felt that the lack of healing was probably due to the fact that the plaster encasement did not give a sufficient and adequate immobilization. In an effort to obtain more rigid immobilization a Stader splint was applied. Active motion was started in the knee and ankle joints, as these joints were badly stiffened due to the long period of plaster immobilization. He was discharged from the hospital with a dressing on the compound wound, bearing some weight and being treated with occupational therapy for joint mobilization. The joint function has improved 75 per cent. The compound wound showed rapid, progressive healing after the splint was applied. The discharge from the wound diminished rapidly and the dressing needed to be changed only every two weeks. The denuded bone covered rapidly with granulation tissue. Roentgenograms, on May 1, 1942, showed a fair amount of callus formation.

It was with great hesitancy that the Stader apparatus was applied in this case because of the infection present at the fracture site. The firm immobilization which the Stader splint produced allowed the infection to subside, reduced hyperemia, and helped callus formation. The seven months of immobilization in plaster caused severe stiffness of the knee and ankle joints and atrophy of the muscles. Mobilization of these joints was possible after the application of the splint. Muscle atrophy was corrected by weight-bearing and active motion at the knee and ankle joints.

Case 4.—A. B., male, age 52, was admitted to the hospital October 26, 1940. Two hours before admission, he had sustained a fracture of the lower third of the left tibia and fibula. A plaster encasement was applied but the position of the frag-

ments was unsatisfactory. A Stader splint was then applied. Due to the small lower fragment, it was impossible to apply two pins in the usual fashion. The splint was then modified to fit this problem by changing the shape of the pin bar so that one pin could be inserted in the lower fragment in an anteroposterior direction and the second pin in the lower fragment could be applied in the usual manner. A curved pin bar was made to fit over these pins. The pins in the upper fragment were applied

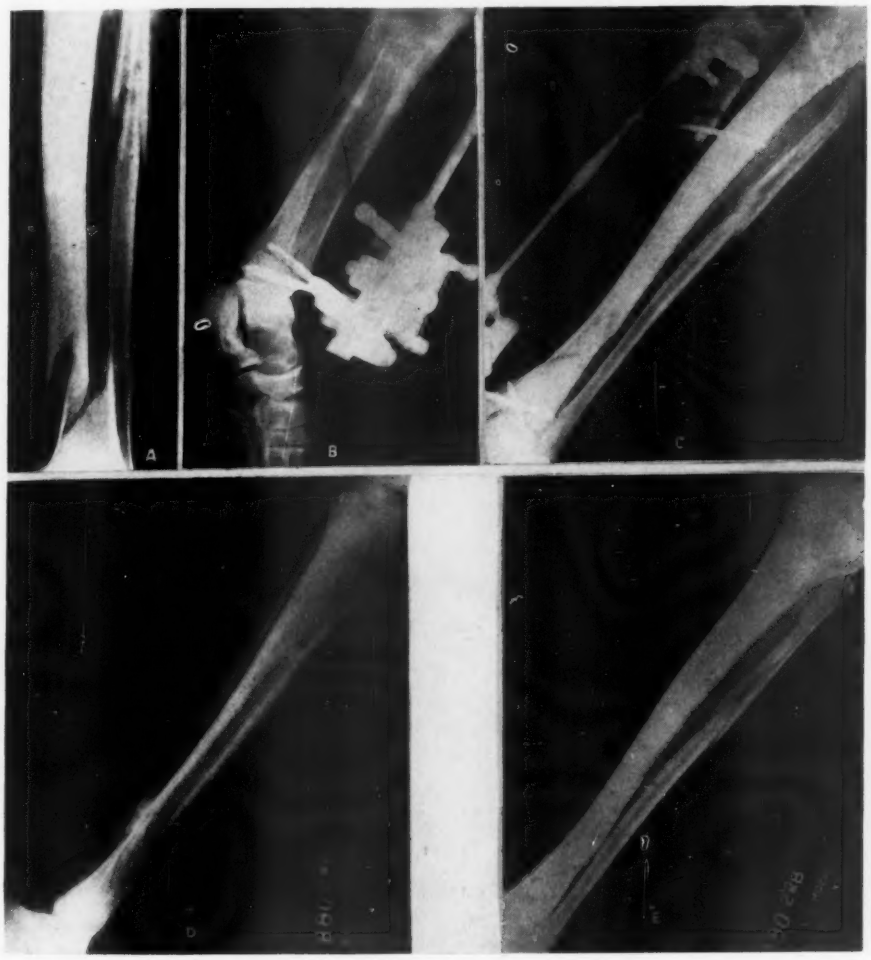


FIG. 8.—Case 4: Fracture of Tibia and Fibula, with a Short Lower Tibial Fragment.
A. Before reduction.
B. and C. Reduction with Stader splint.
D. and E. Showing union, with apparatus removed.

in the usual manner and the standard extension bar fitted to the two pin bars. Adjustments were made and good anatomic alignment secured. The patient walked early, but the apparatus had to be left in place for 210 days before solid union occurred. No further treatment was necessary as the knee and ankle joint had normal range of motion and the pin holes healed in six days (Fig. 8).

The solution of reduction and splinting of fractures very low in the shaft of the tibia and fibula could not be accomplished with the original apparatus

as the bone space which the two lower pins would have to occupy was too short. The apparatus was then modified to be able to apply this method to the very low fractures with short lower fragments.

TABLE I

STATISTICAL DATA OF 20 CASES TREATED WITH THE STADER SPLINT

Name	Sex	Age	Fracture	Apparatus in Place	Days before Union	Seepage	Infection	Complications	End-Result*
E. S.	M.	53	Tibia & fibula	9/20/38–12/6/38	77	Slight, 4 pins	None	None	4-4-4
W. W.	M.	43	Tibia & fibula	10/29/37–1/27/38	91	Slight, 2 pins	None	None	4-4-4
J. M.	M.	53	Tibia & fibula	2/2/38–6/5/38	124	None	None	None	4-4-4
M. S.	F.	52	Tibia & fibula	10/25/38–2/23/39	122	Upper pin	None	None	4-4-4
L. H. (Fig. 9)	M.	53	Tibia & fibula	11/8/38–1/23/39	76	None	None	None	4-4-4
J. L. (Fig. 10)	M.	56	Tibia & fibula (compound)	11/2/38–3/27/39	145	None	None	None	4-4-4
G. G.	M.	47	Humerus	12/26/37–3/5/38	69	None	None	Musculospiral paralysis	4-4-4
A. B.	M.	52	Tibia & fibula	10/30/40–6/11/41	320	None	None	None	4-4-4
H. S.	M.	43	Tibia & fibula; 2 separate fractures	12/21/41–4/1/42	102	Upper pin	None	Intertrochanteric fracture; pubic fracture; alcoholic psychosis	4-4-4
J. H.	M.	43	Tibia & fibula	4/6/41–6/29/41	84	Lower pin	Abscess about lower pin	None	4-4-4
F. G.	M.	28	Tibia & fibula	4/2/40–7/10/40	99	None	None	None	4-4-4
J. B.	F.	38	Tibia & fibula	4/6/40–6/24/40	80	None	None	None	4-4-4
J. B.	M.	70	Tibia & fibula (compound)	2/21/42–present		Three upper pins	None	Diabetes	
A. D.	M.	36	Tibia & fibula (compound)	3/24/42–present		Upper pins	None	Compound fracture	
N. W.	M.	22	Tibia & fibula	4/2/41–6/9/41	68	None	None	None	4-4-4
M. M.	F.	34	Tibia & fibula	10/30/41–1/3/42	65	None	None	Syphilis	4-4-4
J. C.	M.	48	Tibia & fibula	2/7/42–4/23/42	76	Lower pin	Abscess	Abscess; app. removed 4/23/42	4-4-4
R. K.	M.	36	Tibia & fibula	11/29/37–3/31/38	123	Lower pins	None	Frac. malleoli tibia and fibula; frac. skull	4-4-4
C. G.	M.	81	Femur shaft	11/14/37–12/22/37		Upper pins	Abscess about upper pin. Osteomyelitis	Osteomyelitis. Death	Death
M. J.	M.	54	Tibia & fibula (compound)	4/26/40–6/30/40	65	None	None	None	4-4-4

* The end-results have been estimated according to the Massachusetts General Hospital classification. This estimation is made on an anatomic, economic and functional basis: 1 = 25% of normal; 2 = 50% of normal; 3 = 75% of normal; and 4 = 100% of normal.

The headings in Table I are self-explanatory. The column marked seepage does not indicate infection. It means that at the junction that the pin made with the skin there was a small amount of serous discharge,

FIG. 9.—Case L. H.: Fracture of Upper Third of Tibia and Fibula.
A and B. Before reduction.
C. After reduction with Stader splint. Note that the pins in the upper fragment protrude through the distal cortex farther than is to be desired. These pins should have been withdrawn somewhat before they were locked in the pin bar.

FIG. 10.—Case J. L.: Compound Fracture of Middle Third of Tibia and Fibula.
A. Encasement in plaster, showing malposition.
B. Encasement removed—reduction with Stader splint.
C. Showing union—splint removed.

which usually formed a crust about the pin. When the pin was removed, healing occurred within a few weeks. Since the pin bar has been made of a plastic instead of metal the seepage has decreased so that there are 10 cases in which no seepage took place.

This seepage is due to galvanic current set up by the use of two different metals, the pin being stainless steel and the pin bar duralumin. The electrical potential as measured by a galvanometer with the two different metals was as follows:

Between the 1st and 2nd pins	3.5	units
Between the 1st and 3rd pins	2.5	"
Between the 1st and 4th pins	4	"
Between the bar and 1st pin	1.5	"

Between the bar and 2nd pin 1.5 "
Between the bar and 3rd pin 1.5 "
Between the bar and 4th pin 1.5 "

The same readings made with the plastic material for pin bars were:

Between the 1st and 2nd pins 0.5 units
Between the 1st and 3rd pins 0.2 "
Between the 1st and 4th pins 0.2 "
Between the bar and 1st pin 0 "
Between the bar and 2nd pin 0 "
Between the bar and 3rd pin 0 "
Between the bar and 4th pin 0 "

In other words the metal-to-metal contact gives a high dielectric value, whereas with a material of high insulating value the electrical potential is *nil*.

There were three real infections, in two of which abscesses formed and had to be incised and drained. They healed quickly after incision, without any evidence of osteomyelitis. One infection, the femur case, resulted in severe infection with osteomyelitis and death. In this patient, an old man, age 84, the dressings and the pins were continuously contaminated with urine and feces, due to involuntary micturition and defecation. The patient was constantly picking at and removing the dressings, so that it was impossible to avoid secondary contamination of the pin wounds.

CONCLUSIONS

(1) A new splint for reducing and immobilizing fractures of the shafts of the long bones is presented.

(2) Early transportation of the patient is possible, as contrasted to the impossibility of early transportation where traction suspension is used. This is of importance in bombed areas, either in civil or military surgery.

(3) The splint is simple to apply, and correction of malposition of the fragments is possible in all three planes of space even up to the time that fibrous union has occurred.

(4) Early weight-bearing and continued use of the contiguous joints is permitted and urged, and this prevents muscle atrophy and stiffening of the joints from occurring.

(5) After-treatment is reduced to a minimum as muscle strength is retained and joint function carried on.

(6) Seepage around the pins is usually due to galvanism and not to infection. It is not an indication for removing the pins unless accompanying signs of inflammation are present.

REFERENCES

[1] Schanz, A.: München. med. Wchnschr., **69**, No. 25, 930–931, June 23, 1922.
[2] Riedel, G.: Zentralbl. f. Chir., **57**, No. 2, 84–86, January 11, 1930.
[3] Schanz, A.: Arch. f. klin. Chir., **69**, 494–517, 1932.
[4] Stader, O.: North Am. Vet., **18**, No. 1, p. 52.
[5] *Idem*: North Am. Vet., **20**, No. 1, p. 55.
[6] *Idem*: North Am. Vet., **20**, No. 2, p. 54.
[7] *Idem*: North Am. Vet., **20**, No. 3, p. 62.
[8] Parkhill, C.: Trans. Amer. Surg. Asso., **15**, 251, 1897.
[9] Freeman, L.: ANNALS OF SURGERY, **70**, 231, 1919.

BRIEF COMMUNICATION

A NEW RECTOSIGMOIDAL BIOPSY FORCEPS

ROBERT TURELL, M.D.

NEW YORK, N. Y.

THE INSTRUMENT, illustrated in Figure 1, is designed primarily for obtaining rectal and sigmoidal biopsy specimens. This biopsy specimen forceps embodies several new features. The shaft with the cutting jaws at its distal end has a rotating mechanism with a locking device near the handle, permitting 360 degrees rotation of the jaws. Thus, the shaft of the forceps can be rotated so that the cutting jaws will face directly a suspected lesion located anywhere in the circumference of the rectum or sigmoid (Fig. 2). Furthermore, the cutting jaw mechanism operates at an angle of about 30 degrees from the axis of the shaft and consists of a stationary and a

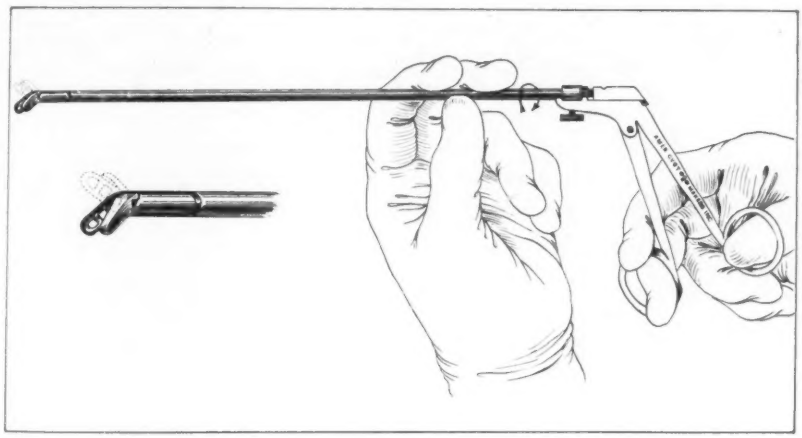


FIG. 1.—Showing the biopsy forceps and a diagrammatic view of the rotary movement of the shaft.

moving jaw, the latter opening and closing sidewise (Fig. 2A). The sidewise operation of the moving jaw makes for better visualization of the tissue engaged in the cutting jaws until they are closed (Fig. 3); this is especially true in the case of the small polypoid lesions. Thus, with this biopsy specimen forceps, mucosal excrescences and small sessile or pedunculated adenomata can be removed for microscopic study with ease and safety prior to fulguration.*

* I have emphasized the clinical importance of these lesions in a recent review of the literature (Am. J. M. Sc., **202**, 282, August, 1941) by showing that many authorities regard mucosal excrescences and polypi of the rectum and sigmoid as precursors of frank malignancies in certain cases.

The biopsy forceps herein described is equipped with scissors handles to apply positive pressure for opening and closing the jaws. The moving jaw fits inside the cutting edge of the stationary one, thus assuring a clean-cut specimen by the shearing action of the jaws; no overhanging lips interfere with the clean excision of tissue. The jaw capacity is ample; the stationary

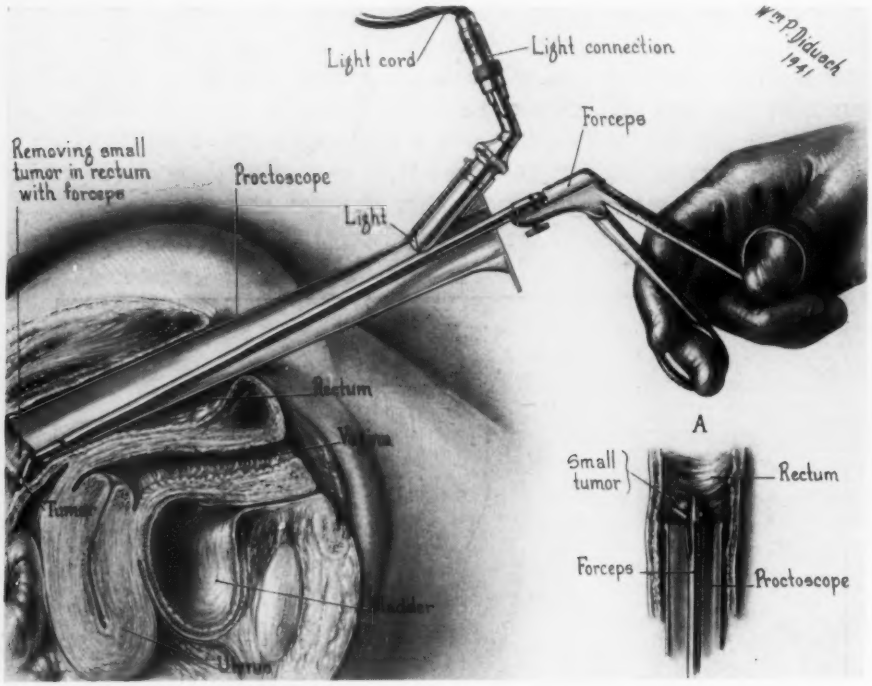


FIG. 2.—Sagittal section showing the removal of a small sessile polyp with forceps. (A) Showing angle of jaws of forceps as viewed from above.

jaw has two openings to prevent the crushing and distortion of the specimen. At the same time the bars formed between those openings prevent the loss of the excised specimen. The instrument is sturdily built and is manufactured in different working lengths; the one illustrated here is 40 cm. long.

My thanks are due to Mr. F. C. Wappler and Mr. H. S. Rubens, of the American Cystoscope Makers, Inc., New York, N. Y., for their technical advice, and to Mr. W. P. Didusch for the illustrations.

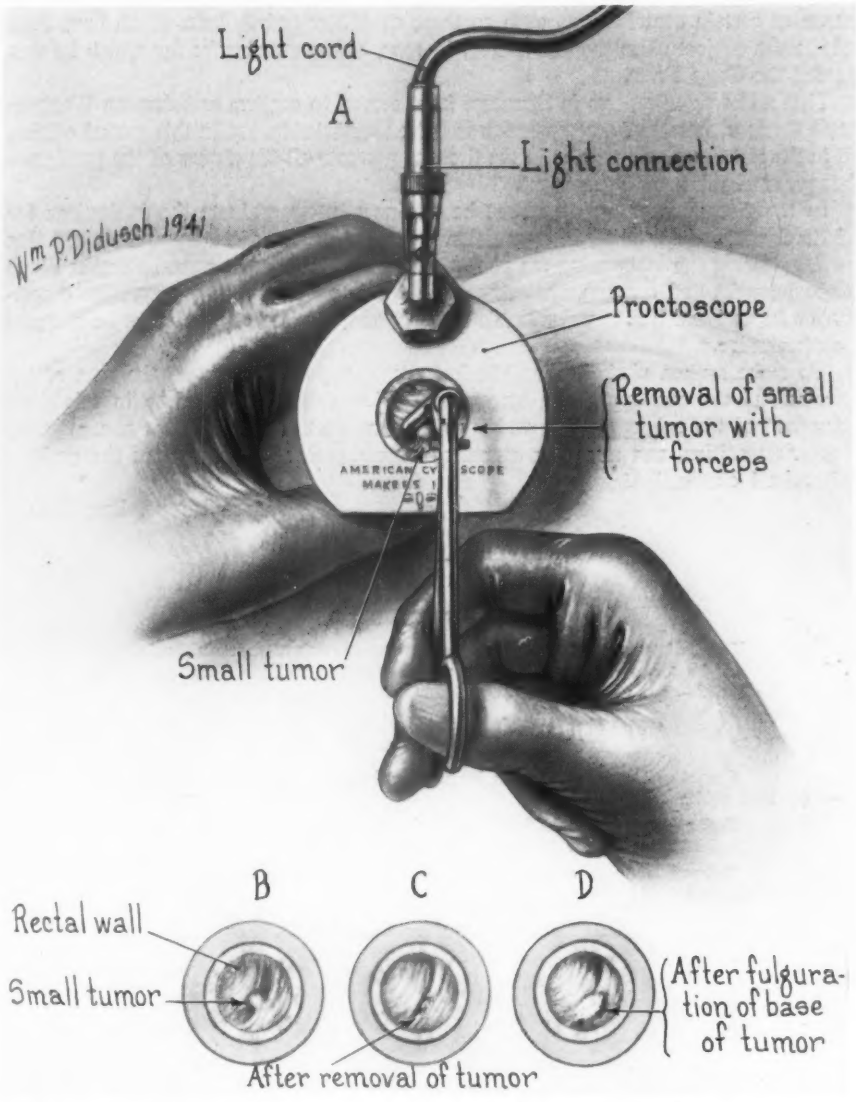


FIG. 3.—(A) Actual view of tumor in relation to the jaws of forceps. (B) View of tumor *in situ*. (C) Appearance of base of tumor after removal. (D) Appearance of base of tumor after coagulation.

BOOK REVIEW

INTESTINAL OBSTRUCTIONS. (Second Edition) BY OWEN H. WANGENSTEEN, M. D.

Published by Charles C. Thomas—1942

A second edition of Wangensteen's monograph on Intestinal Obstruction is timely because of certain contributions, such as those of Miller and Abbott, which have been made to the subject since the publication, in 1932, of the manuscript for which he was awarded the Gross Prize.

That all of these reports in literature have served to confirm and develop Wangensteen's thesis of intestinal decompression is indeed remarkable, but in this second edition, and in the same masterly way as in the first, he presents all the phases of the problem—etiology, mechanism, and treatment.

In the discussion of the treatment he can now better evaluate the indications for and the dangers of intestinal decompression by tubes, because of his experience and that of others during the intervening ten years. His statement, that it must be realized both by the internist and surgeon, that there is a limit to the use of conservative decompression beyond which it is unjustifiable to delay surgical intervention, must be accepted as authoritative.

To make such a vital decision requires complete collaboration on the part of the internist and the surgeon, and Wangensteen makes this perfectly clear in this "new testament" of his original essay, which is without question essential as a supplement to the first edition, and also as a summary of our present knowledge of the problem of intestinal obstruction.

WALTER ESTELL LEE, M.D.

EDITORIAL ADDRESS

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PLATE I

Colored photographs of a burn treated by the author's technique.

The top picture shows a three-day infected superficial burn of the face and slightly deeper burn of the dorsum of the hand and wrist. This picture was taken on the day following night admission, the burn having been cleaned and dressed during the night. The dressing was removed for the picture. Below it are pictures of the face on the 4th and 12th day after admission, when healing was complete; and pictures of the hand on the 4th, 8th and 12th days, when epithelization was complete and only a protective cotton gauze was needed.